LETTERS

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- $\alpha_{\mu}\beta$ -unsaturated γ -lactams via a C–S bond activation,



isocyanide migratory insertion, hydrogenation, selective aerobic oxidation, and intramolecular nucleophilic addition sequence.

P alladium-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 dithioacetals¹² 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 dithioacetals¹¹ 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 crosscoupling 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 5hydroxy- $\alpha_{\beta}\beta$ -unsaturated γ -lactams, a class of important Nheterocycles.¹

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(PPh₃)₂Cl₂ in the presence of 2 equiv of Ph₃SiH 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 H₂O in the solvent followed by an intramolecular nucleophilic addition. However, additional water made the reaction sluggish

Scheme 1. Pd-Catalyzed Isocyanide Insertion and Transformations



due to the significant decomposition of 4-PhC₆H₄NC in DMSO-H₂O mixed solvent (Scheme 2A-(2)). Other isocyanides, including PhCH₂NC, EtO₂CCH₂NC, *t*BuNC, and TsCH₂NC, were then subject to this catalytic system in the presence of H₂O. It was found that EtO₂CCH₂NC 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 TsCH₂NC (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 EtO₂CCH₂NC 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)).

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^{*a*}Reaction conditions: **1a** (0.5 mmol), R'NC (3 equiv), Pd(PPh₃)₂Cl₂ (10 mol %), Ph₃SiH (2 equiv), DMSO (5 mL), N₂, 90 °C. Isolated yield.

Thus, we chose EtO_2CCH_2NC for screening the reaction conditions. It was found that 5 mol % of Pd(PPh₃)₂Cl₂ 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



^{*a*}Reaction condition: **1a** (0.5 mmol), EtO₂CCH₂NC (3 equiv), solvent (5 mL), H₂O (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*}EtO₂CCH₂NC (1.5 equiv). 51% of **1a** was recovered.

using 1.2 equiv of Ph₃SiH (entry 5). Prolonging the reaction time led to more **5a** (entry 6), and decreasing the amount of EtO_2CCH_2NC 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(PPh₃)₂Cl₂ in DMSO (entries 8–14).

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

Table 2. Scope of Ketene Dithioacetals $1^{a,b}$

R ² RS		EtO2CCH2 NC Pd(PPh3)2Cl2/Ph3Sih DMSO-H2O, N2	+		H :R' :R' = Cl	H ₂ CO ₂ Et
entry	\mathbb{R}^1	\mathbb{R}^2	R	time (h)	3	yield (%) ^b
1	Me	$4-FC_6H_4$	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	$2-FC_6H_4$	Et	5	3f	87
7	Me	$4-FC_6H_4$	Bn	6	3g	72
8	Me	$4-FC_6H_4$	Me	3	3h	81
9	Me	4-ClC ₆ H ₄	Me	3	3i	79
10	Me	Me	Me	5	3j	83
11	Me	Н	Et	5	3k	58
12	Me	PhCO	Et	4	31	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	30	77
16	Ph	Ph	Et	16	3p	65
17	Ph	PhCO	Et	5	3q	83 ^c
18	Н	4-MeOC ₆ H ₄	Et	6	3r	complex
^{<i>a</i>} Reaction condition: 1 (0.5 mmol), EtO_2CCH_2NC (3 equiv), $Pd(PPh_3)_2Cl_2$ (5 mol %), Ph_3SiH (1.2 equiv), DMSO (5 mL), H_2O (0.5 mL), 70 °C. ^{<i>b</i>} Isolated yield. ^{<i>c</i>} Ph_3SiH (2 equiv), 90 °C.						

as substrates for the Pd-catalyzed imidovlation reaction. On one hand, aromatic \mathbb{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 11-n with an α -carbonyl. On the other hand, the reactions of 10-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 \mathbf{lr} (R¹ = 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 N₂. However, no ¹⁸O-labeled **3a** was observed in its HRMS analysis. Another reaction which was quenched by $H_2^{18}O$ did not afford ¹⁸O-labeled **3a** either. The results ruled out a

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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 ¹⁸O₂ after **1a** was consumed in the [Pd]/[SiH] catalytic system under N₂. ¹⁸O-Labeled **3a** was detected by HRMS.

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 N₂ 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 Ph₃SiH produced imidoyl-Pd-H C along with the release of Ph₃Si-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 H₂O. 3 were formed by a tandem aerobic oxidation of D leading to oxaziridine E_{ν}^{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 tertbutyl 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 = 360.0657assigned 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 Ph₃SiH could afford 3a but in less than 30% yield under standard conditions. In this case, a protodepalladation of \mathbf{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 **3I** 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- $\alpha_{,}\beta$ -unsaturated γ -lactams 7 were isolated in good yields.



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 O₂ 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.or-glett.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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