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Palladium-Catalyzed Intramolecular Selenocarbamoylation of Allenes with Carbamoselenoates: A New Entry to α,β-Unsaturated Lactams

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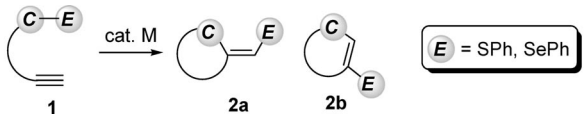
Keywords: Cycloaddition / Lactams / Allenes / Selenium / Allylic compounds

$Pd(PPh_3)_4$-catalyzed intramolecular selenocarbamoylation of allenes led to the regioselective formation of α,β-unsaturated five- and six-membered lactams having an allyl selenide unit. This procedure could be applied to the synthesis of the corresponding sulfur analogue by thiocarbamoylation as well as a cyclopentenone.

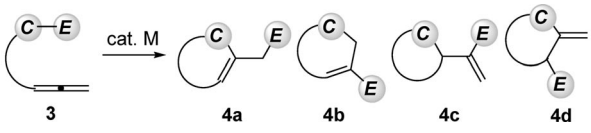
Introduction

Previously, we had developed a transition-metal-catalyzed intramolecular cyclization by cleavage of carbon–chalcogen (sulfur or selenium) bonds and subsequent addition to alkynes.[1] In this system, the insertion of an alkyne into a C–E (E = S or Se) bond would proceed regioselectively to give cyclic products like **2a** having an *exo*-methylene moiety without the formation of its regioisomer **2b** [Equation (1)].

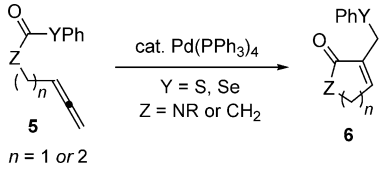


(1)

When this catalytic system is applied to allenes **3**, four possible products **4a**–**d** can be formed [Equation (2)]. Recently, we also disclosed that selenol esters, a selenocarbonate and a carbamoselenoate added regioselectively to the distal double bond of terminal allenes in the presence of a Pd^0 catalyst to give rise to conjugated allyl selenides.[2] These facts led us to hypothesize that intramolecular cyclization using allenic substrates **3** took place efficiently to afford cyclic products **4a** having a double bond in the ring system [Equation (2)]. Although intramolecular addition of a carbon–hydrogen bond to the allene unit is well known and employed for cyclization of allenes,[3] intramolecular insertion of allenes into carbon–heteroatom bonds has not been studied extensively.[4] We thus examined the intramolecular variation of selenocarbamoylation of allenes aiming at an efficient construction of α,β-unsaturated lactam frameworks that are core structures of several pharmacologically active compounds and useful as synthetic intermediates [Equation (3)].[5]



(2)



(3)

Results and Discussion

At first we carried out the reaction of carbamoselenoate **5a** (Z = NBn, *n* = 1) possessing a terminal allene unit on the nitrogen atom under typical reaction conditions employed for the corresponding intermolecular system.[2] When toluene (0.5 mL) containing carbamoselenoate **5a** (0.4 mmol) and $Pd(PPh_3)_4$ (5 mol-%) was heated at 110 °C for 5 h, an α,β-unsaturated five-membered lactam **6a** was obtained in 50% yield along with 24% of an unexpected six-membered lactam **7** (without an SePh group) as a by-product.

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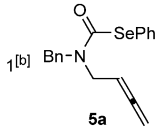
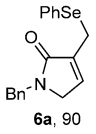
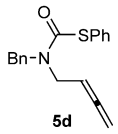
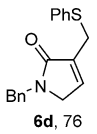
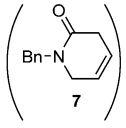
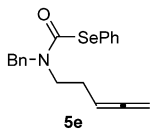
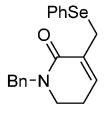
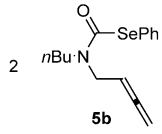
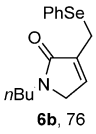
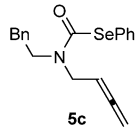
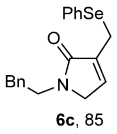
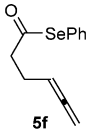
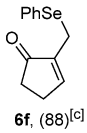
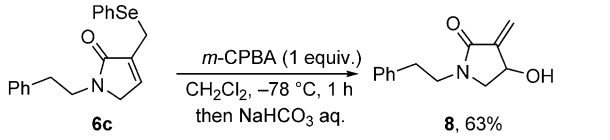
By changing the solvent, five-membered lactams were found to be formed selectively and efficiently. For example, the reaction of carbamoselenoate **5a** in DMF at 80 °C for 5 h afforded lactam **6a** in 90% yield without formation of unexpected lactam **7** (Table 1, Entry 1). Results obtained with several substrates are also summarized in Table 1.[6] Similar γ-lactams **6b** and **6c** were formed readily in high yields indicating that the substituent on the N-atom does not affect the reaction (Entries 1–3). This cyclization system could be applied to intramolecular thiocarbamoylation to give the corresponding allyl sulfide **6d** in high yield (Entry 4). The six-membered lactam **6e** was also obtained in good yield under similar reaction conditions with perfect regioselectivity when carbamoselenoate **5e** was employed. In contrast to the reaction of **5a**, compound **5e** afforded **6e** selectively even in refluxing toluene, and a by-product like **7** was not detected (Entry 5). Similarly, the cyclopentenone ring could be constructed selectively in toluene (Entry 6).[7] For all runs listed in Table 1, no regioisomer of **6**, which may arise by the addition to the inner double bond of the allene unit, was detected.

Table 1. Intramolecular cyclization of **5** to form products **6** [Equation (3)].[a]

Entry	5	6, Isolated yield (%)	Entry	5	6, Isolated yield (%)
1[b]		 **6a**, 90	4		 **6d**, 76
		 **7**	5		 **6e**, 82 (75)[c]
2		 **6b**, 76			
3		 **6c**, 85	6		 **6f**, (88)[c]
	5a			**5d**	
	5b			**5e**	
	5c			**5f**	

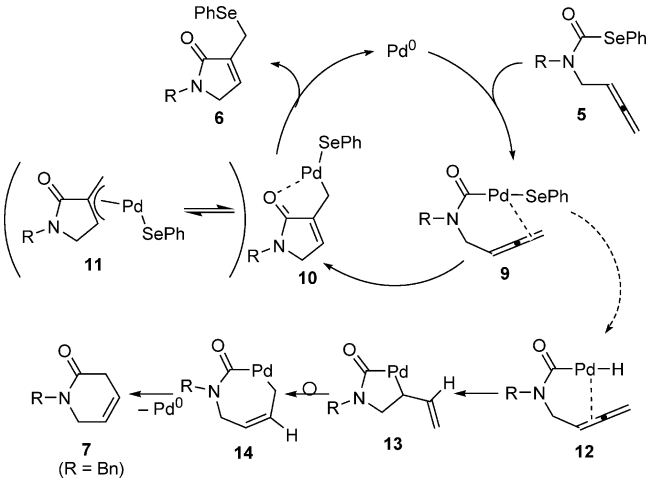
[a] Conditions: **5** (0.40 mmol), $Pd(PPh_3)_4$ (5 mol-%), DMF (0.5 mL), 80 °C, 5 h. [b] Reaction time 1 h. [c] Yields in parentheses were obtained by reactions in toluene at 110 °C for 5 h (Entry 5) or 0.5 h (Entry 6).

As a synthetic transformation of these products,[8–10] **6c** was converted into allyl alcohol **8** by oxidation with *m*-CPBA followed by hydrolysis [Equation (4)].



(4)

Plausible reaction pathways leading to the lactam **6** and to the by-product **7** are shown in Scheme 1.



Scheme 1. Plausible reacttion pathways to **6** and **7**.

The first step in these reactions is an oxidative addition of the carbamoyl–Se bond of carbamoselenoates **5** to Pd^0 giving rise to the allene-coordinated complexes **9**. Subsequent insertion of a distal C=C double bond from the coordinated allene into the carbamoyl–Pd bond generates the (σ-allyl)palladium species **10**, which may be in equilibrium with the (π-allyl)palladium species **11**.[2] Reductive elimination leads to the five-membered lactams **6**, and Pd^0 is regenerated.[11] Although the mech **12** may account for the pathway. Hydropalladation of the proximal C=C double bond forms five-membered palladacycle **13** as an intermediate.[3c,3d] Isomerization of **13** to seven-membered compound **14** via a π-allyl complex occurred followed by reductive elimination to afford **7**. To shed light on the carbopalladation pathway (from **9** to **10**, Scheme 1), DFT calculations were conducted for the model structures **A**, **B** and **TS** shown in Figure 1.

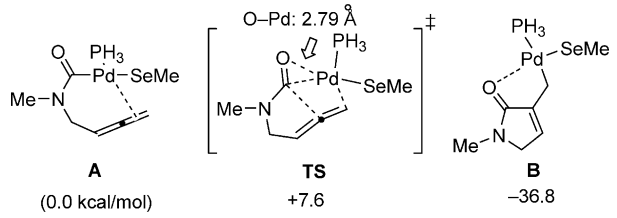
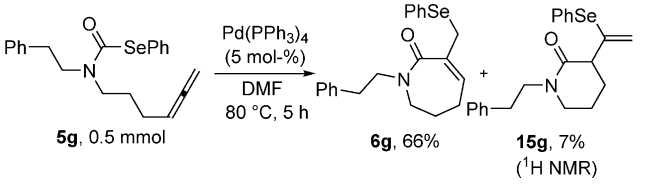


Figure 1. Calculation models.

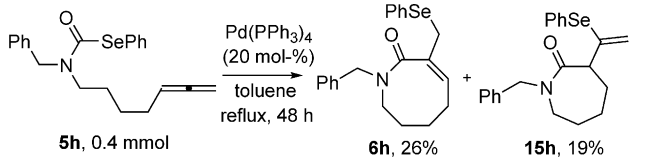
As demonstrated in the case of intermolecular selenoacylation of allenes,[2] the distance from O to Pd in **TS** (2.79 Å) is shorter than the sum of van der Waals radii of O and Pd (3.15 Å): Intramolecular coordination of the carbonyl oxygen atom towards the palladium atom may stabilize **TS**.

The synthesis of medium-sized lactams was also examined. The reaction of carbamoselenoate **5g** that has a 4,5-hexadienyl group on the nitrogen atom gave the seven-mem-

bered lactam **6g** in 66% yield [Equation (5)]. The six-membered lactam **15g** was, however, also obtained in 7% yield concomitantly. When the isolated compound **6g** was subjected to the same reaction conditions as of Equation (5) no isomerization to **15g** occurred. In the case of carbamoselenoate **5h**, having a 5,6-heptadienyl group, both an eight-membered lactam **6h** and a seven-membered lactam **15h** were formed in low yields with poor selectivity even when 20 mol-% catalyst was used [Equation (6)].[12] As described above (see Scheme 1), desired medium-sized lactams **6g**–**h** are formed through (σ-allyl)palladium species **17a** by carbopalladation of the distal double bond of the allenes. Carbopalladation of the proximal double bond, giving carbonyl-chelated vinyl palladium complexes like **17b**, is a possible pathway that leads to minor products **15g**–**h**. Product ratio would be determined by the relative stabilities of **17a** and **17b** (Figure 2).



(5)



(6)

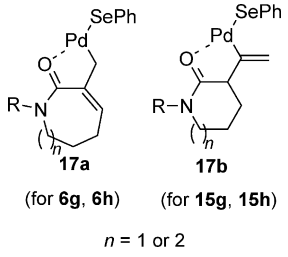


Figure 2. Possible intermediates.

Conclusions

We report that intramolecular selenocarbamoylation of allenes proceeds in the presence of Pd^0 catalyst producing α,β-unsaturated γ- and δ-lactams with perfect regioselectivity. This cyclization could also be applied to thiocarbamoylation and to the construction of a cyclopentenone framework. Intramolecular addition of carbon–selenium bonds to the allene unit takes place selectively giving rise to the formation of allyl selenides. Although allyl selenides are known to react with transition metals, further reactions such as oligomerization of allenes were not observed in this system.[2,13]

Experimental Section

1-Benzyl-3-(phenylselenomethyl)-1,5-dihydropyrrol-2-one (6a). Typical Procedure: Into a 3-mL flask equipped with a reflux condenser were placed carbamoselenoate **5a** (0.41 mmol, 140 mg), DMF (0.4 mL) and $Pd(PPh_3)_4$ (0.020 mmol, 24 mg) at room temperature under N_2, and the solution turned immediately red. After the mixture was heated at 80 °C for 5 h, filtered through a Celite pad with Et_2O, volatiles were removed in vacuo. The crude product was purified by preparative TLC (*n*-hexane/Et_2O, 1:1) to afford **6a** in 90% yield (126 mg) as brown oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.65 (s, 2 H), 3.75 (s, 2 H), 4.62 (s, 2 H), 6.47 (s, 1 H) 7.19–7.51 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3, 46.4, 50.0, 127.4, 127.6, 128.0, 128.7, 129.0, 130.0, 133.7, 136.4, 136.5, 137.2, 170.1 ppm. IR (NaCl): $\tilde{\nu}$ = 3060, 2917, 1682 (C=O), 1452, 1244, 1077, 817, 738, 693 cm^{-1}. MS (EI): *m*/*z* (%) = 343 (2) [M^+], 185 (40), 91 (100). HRMS (EI): calcd. for $C_{18}H_{17}NOSe$ 343.0475; found 343.0478. Copies of ^1H and ^{13}C NMR spectra of **6a** in $CDCl_3$ are shown in the Supporting Information.

Supporting Information (see footnote on the first page of this article): Experimental and calculation details and characterization data of all new compounds.

Acknowledgments

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[2] M. Toyofuku, E. Murase, S. Fujiwara, T. Shin-ike, H. Kuniyasu, N. Kambe, *Org. Lett.* **2008**, *10*, 3957–3960.

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[6] The solvent effect was examined by using **5b** as a substrate. NMR yields of **6b** obtained in 5 h are as follows: 38% (toluene, reflux), 14% (toluene, 80 °C), 35% [cyclopentyl methyl ether (CPME), 80 °C], 60% (THF, reflux), 83% (PhCN, 80 °C), 86% (DMF, 80 °C). The order of the yields coincides with that of the polarity of solvents: Dielectric constants (ε_r, 25 °C) of the solvents: toluene (2.38), CPME (4.76), THF (7.58), PhCN (25.20), DMF (36.71), see: a) C. Reichardt, *Solvents and Solvent Effects in Organic Chemistry*, 3rd ed., Wiley-VCH, Weinheim, **2003**; b) K. M. Kadish, J. E. Anderson, *Pure Appl. Chem.* **1987**, *59*, 703–714; c) K. Watanabe, N. Yamagiwa, Y. Torisawa, *Org. Process Res. Dev.* **2007**, *11*, 251–258.

[7] When the reaction of **5a** was conducted in [D_8]toluene at 110 °C, no deuterium-incorporated products were detected. When 1 equiv. of fluorene or H_2O were added as possible H-sources, product selectivities (**7** vs. **6a**) were not changed. From these results, allylic hydrogen atoms in the ring (α-hydrogen atoms of the nitrogen atom) of the products would be the H-source forming **7**. Selective formation of **6e** and **6f** from **5e** and **5f** in refluxing toluene (Entries 5 and 6), where allylic hydrogen atoms in the ring of **6e** and **6f** located at the β-carbon atom also support this hypothesis.

[8] Allyl selenides are recognized not only as versatile synthetic intermediates (ref.[9]) but also as potential mimetics of enzyme and precursors of DNA radicals (ref.[10]).

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[11] Facile reductive elimination of allyl selenides from (allyl)palladium intermediates was proposed in the catalytic deoxycarbonylation of allylic selenocarbonates; see ref.[9g]

[12] Although **5h** was comsumed completely, an unseparatable complex mixture containing oligomers of the allene unit was obtained besides **6h** and **15h**.

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