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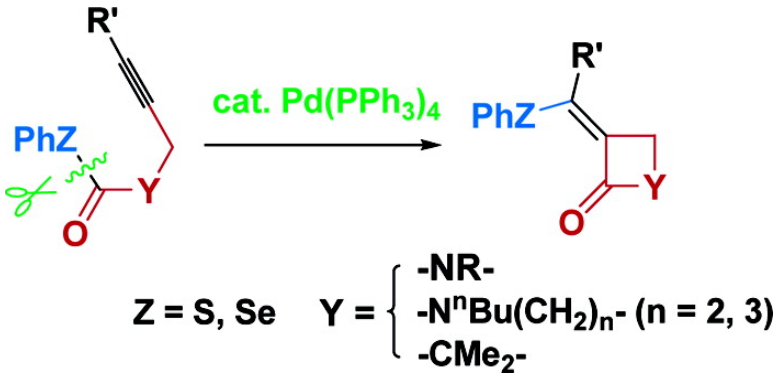

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Palladium-Catalyzed Intramolecular Selenocarbamoylation of Alkynes with Carbamoselenoates: Formation of α-Alkylidene-β-lactam Framework

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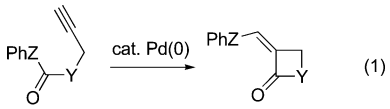
Transition-metal-catalyzed addition of organochalcogen compounds to alkynes with cleavage of bonds such as RS−SR′, RS−BR′$_2$, RSe−P(O)(OR′)$_2$, etc. is a promising synthetic route to functionalized alkenes. This chemistry has been studied extensively.[1−3] Although the more attractive and challenging theme of interest would be the insertion of C−C unsaturated units across chalcogen−carbon bonds that can construct new chalcogen−carbon and carbon−carbon bonds in one step, this transformation remains much less explored.[4−8] To the best of our knowledge, the first example of this type of reactions was found by Ando and co-workers, who reported Pd-catalyzed insertion of dimethyl acetylenedicarboxylate (DMAD) into the S−C bond of allene episulfides to give cyclic products in low yields.[4] Meng and co-workers reported Cu-catalyzed seleno- and telluroacylation of alkynes with selenol and tellurol esters (ArSe−C(O)R and ArTe−C(O)R), respectively, via nucleophilic addition of in situ generated copper acetylides to chalcogeno esters.[5] Tanaka and co-workers revealed Pd-catalyzed thioesterification of alkynes through oxidative addition of thiocarbonate (PhS−C(O)OMe) to Pd in the presence of a bulky trialkyl phosphine.[6] We also have shown that thiol esters (ArS−C(O)R)[7] and selenol esters[8] undergo decarbonylative addition to alkynes in the presence of Pt catalysts. These transformations produce vinyl chalcogenides; this work also demonstrates that selenoacylation proceeds competitively in the case of some selenol esters.

Here we disclose that Pd catalyzes intramolecular selenocarbamoylation of alkynes to give α-alkylidenelactams.



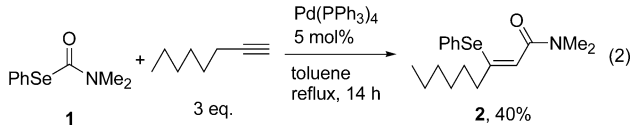
(1)

Z = Se, S

Y = -NR-, -N^{n}Bu(CH$_2$)$_n$- (n = 2, 3), -CMe$_2$-

Since it has been reported that the reaction of a carbamothioate, PhS−C(O)NMe$_2$, with 1-pentyne does not proceed efficiently in the presence of Pd(PPh$_3$)$_4$,[9a] we first examined the possibility of selenocarbamoylation by reacting a carbamoselenoate, PhSe−C(O)-NMe$_2$ (**1**), with an alkyne. When toluene (0.3 mL) containing **1** (0.5 mmol), 1-octyne (3 equiv), and Pd(PPh$_3$)$_4$ (5 mol %) was heated at reflux for 14 h, the selenocarbamoylation product, β-seleno acrylamide **2**, was obtained in 40% yield with high regio- and stereoselectivity (eq 2).

This finding led us to examine the construction of the α-alkylidene-β-lactam framework, a core structure of several antibiotics and various synthetic intermediates, by applying this reaction using an intramolecular cyclization strategy.[10−12] Our working hypothesis for α-alkylidene-β-lactam synthesis is shown in Scheme 1. The

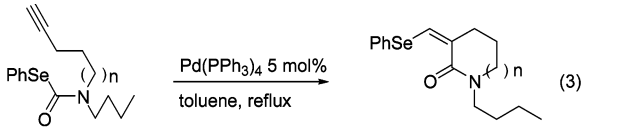


1 **2**, 40% (2)

first step in this process is oxidative addition of the Se−CON bond of **3** to Pd(0) giving **5** via **4** or **4′**. Subsequent insertion of alkyne into the Se−Pd bond affords the five-membered palladacyle **6**.[13] Reductive elimination leads to the cyclized products **7** and regenerates the Pd(0) species.

When *Se*-phenyl *N*-methyl-*N*-prop-2-ynyl carbamoselenoate **3a** (0.4 mmol) was treated with Pd(PPh$_3$)$_4$ (5 mol %) in toluene (0.5 mL) at reflux, the corresponding α-alkylidene-β-lactam **7a** was formed in 74% yield within 1 h with excellent regio- and stereoselectivity (Table 1, run 1).[14] The results obtained using several carbamoselenoates are also summarized in Table 1. This reaction proceeds efficiently even when the amount of Pd(PPh$_3$)$_4$ is reduced to 1 mol % (run 2). Bulkier alkyl substituents on nitrogen, e.g., butyl or benzyl, did not affect the reaction (runs 3 and 4). In contrast to the fact that internal alkynes are sluggish in thioesterification reactions,[6a] carbamoselenoates **3d** and **3e** having an internal alkyne moiety readily undergo intramolecular selenocarbamoylation to afford the desired lactams **7d** and **7e** in high yields (runs 5 and 6, respectively). The structures of products were confirmed by either NOE experiments or X-ray analysis, and the *E*/*Z* ratios were determined by ^{1}H NMR.

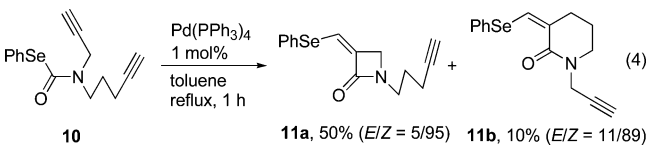
This reaction was also applied successfully to the construction of the α-alkylidene-δ-lactam and -ϵ-lactam frameworks.[15] When carbamoselenoates **8** having a 4-pentynyl or a 5-hexynyl group on the N atom were treated under similar conditions, six- and seven-membered lactams **9** were obtained in high yields (eq 3).



8a: n = 1
8b: n = 2

9a: n =1, 1 h, 75% (*E*/*Z* = 0/100)
9b: n = 2, 12 h, 74% (*E*/*Z* = 0/100) (3)

Very interestingly, when carbamoselenoate **10** having both 2-propynyl and 4-pentynyl groups on the N atom was employed, the more strained four-membered lactam **11a** was obtained predominantly (50%) over the more thermodynamically stable six-membered lactam **11b** (10%) (eq 4). This result indicates that formation of the four-membered ring is kinetically favored.



10 **11a**, 50% (*E*/*Z* = 5/95) **11b**, 10% (*E*/*Z* = 11/89) (4)

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Scheme 1. A Proposed Pathway for α-Alkylidene-β-lactam **7**

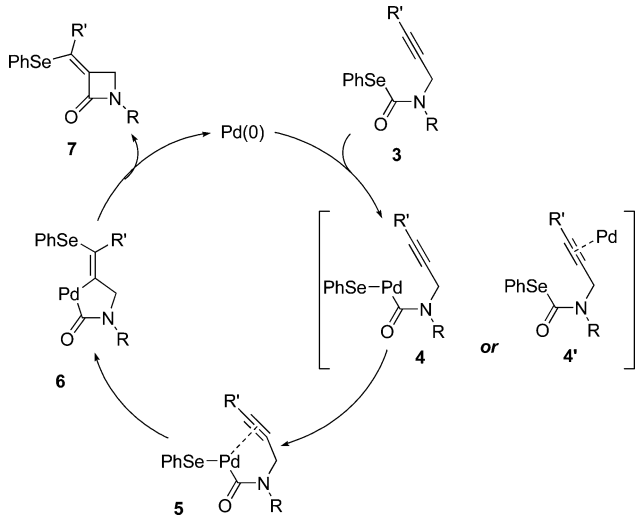


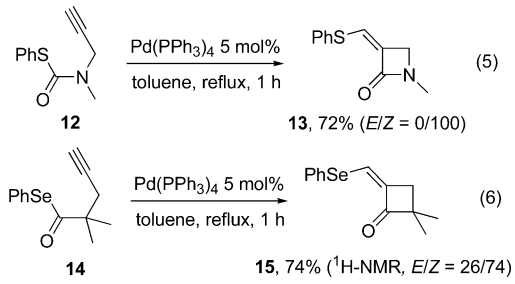
Table 1. Intramolecular Cyclization of **3** to Form **7**[a]

run	3	R	R′	isolated yield (NMR yield) of **7**	*E*/*Z*
1	**3a**	Me	H	74%	0/100
2[b]	**3a**	Me	H	81%	0/100
3[c]	**3b**	^{n}Bu	H	60% (85%)	2/98
4	**3c**	Bn	H	59% (84%)	3/97
5[c]	**3d**	Bn	Et	88% (94%)	3/97
6[d]	**3e**	Me	4-ClC_6H_4	76%	11/89

[a] Conditions: **3** (0.4 mmol), $Pd(PPh_3)_4$ (5 mol %), toluene (2 mL), reflux, 1 h. [b] $Pd(PPh_3)_4$ (1 mol %). [c] Toluene (0.5 mL). [d] Toluene (4 mL), 20 h.

Although all attempts to directly observe the intermediates by ^1H and ^{31}P NMR in a stoichiometric mixture of **3a** and $Pd(PPh_3)_4$ failed, we propose that coordination of the internal C−C triple bond to Pd[16] occurs prior to or after the oxidative addition of the Se−C bond to Pd (via **4′** or **4** in Scheme 1, respectively), leading to **5**.

Meyer and Knapton recently developed a Pd-catalyzed four-component coupling reaction of sulfonamides with diselenides, alkynes, and carbon monoxide to give β-seleno acrylamides.[9] They also claimed that thiocarbamoylation of 1-pentyne with $PhSC(O)NMe_2$ was sluggish (<5%).[9a] On the other hand, intramolecular thiocarbamoylation took place efficiently under similar reaction conditions as shown in eq 5. Intramolecular Pd-catalyzed seleno-



acylation also proceeded efficiently to give 2-methylidene cyclobutanone **15** in high yield from selenol ester **14** (eq 6).[17]

In summary, $Pd(PPh_3)_4$ catalyzes intermolecular selenocarbamoylation of 1-octyne with carbomoselenoate **1** to afford a β-seleno acrylamide in a moderate yield. This catalytic system can successfully be applied to intramolecular systems giving rise to the conjugated lactams and a cyclobutanone having seleno and thio substituted *exo* methylene groups at the α-carbon. A significant role of alkyne coordination to Pd in this catalytic reaction is proposed.

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Supporting Information Available: Experimental details and characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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