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Communication

Palladium-Catalyzed Cyclization

Cyclative Cascades of Allenamides Derived from Amino Acids: Synthesis of Annulated Indoxyl Derivatives

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Abstract: Allenamides derived from amino acids participate in the cascade transformations catalyzed by Pd^0 allowing consecutive formation of two five-membered rings. The developed methodology provides an access to annulated indoles which can be transformed to functionalized indoxyl derivatives, retaining a structural motif embedded in several natural products.

Introduction

Allenamides are versatile synthetic blocks, which have been extensively studied in recent years.[1–11] They undergo numerous transformations providing access to diverse structural motifs.[12–15] Amongst the reactions of allenamides, particularly interesting are cascade processes promoted by transition metals.[3,16–21] They allow the creation of several bonds in a single operation permitting access to complex molecules from relatively simple starting materials. The utilization of Pd^0 catalysis for these purposes is arguably on the forefront in this area.[21–31] Strategically, numerous cascades of allenamides have been developed, usually initiated with the formation of a π-allylpalladium intermediate followed by anion capture, β-hydride elimination/cycloaddition, transmetallation/nucleophilic addition or coupling with organometallic reagents. Recently, Pd^{II}-promoted cyclizations of allenamides onto the alkene have also been reported.[32]

The fact that the simple allenamides may afford complex structures often in a one-pot process prompted us to study their application in the synthesis of a 1,2-annulated indoxyl skeleton, which is a structural arrangement present in many natural products (Figure 1).[33–37] More precisely, we intended to explore the transformation outlined in Scheme 1, which would involve the formation of a five-membered ring by initial Pd^0-catalyzed cyclization followed by a second cyclization through nucleophilic displacement to form an additional five-membered ring. The process would also create an exocyclic double bond, which could be further transformed into a keto functionality leading to an indoxyl skeleton present in many natural products. This tactical variation in transforming allenamides by combining two intramolecular steps has been previously reported but never explored in a consecutive formation of two condensed five-membered rings.[23,38] An additional problem would arise from the potential isomerization of the double bond to form indole, which would prevent the installation of the oxygen functionality to form **2b** in a straightforward manner. Encouragingly, some recent results demonstrated the usefulness of compounds related to **2a** in the synthesis of several indole-derived natural products.[39]

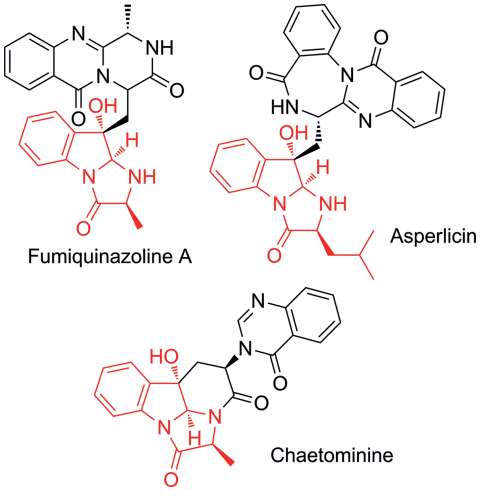
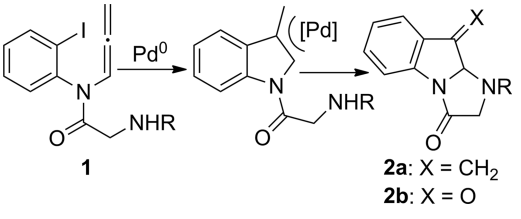


Figure 1. Examples of natural products.



Scheme 1. Proposed cyclization of allenamides.

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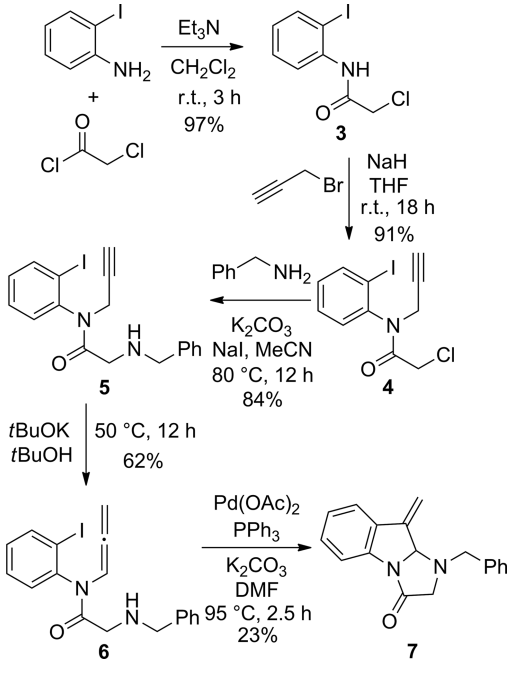
Results and Discussion

The initial allene substrate **6** used in this study was prepared starting from iodoaniline as outlined in Scheme 2. Several standard transformations afforded propargyl derivative **5** in good overall yield. The propargyl/allenyl isomerization leading to allene **6** proved to be somewhat challenging. The early isomerization reactions were performed in THF with various quantities of *t*BuOK (0.2–5 equiv.).[40,41] Although the product was formed in most cases, the yields were low, and often the conversion was incomplete. A further problem was caused by side products, which were the result of a cyclization reaction due to the presence of the nucleophilic secondary amine functionality.[42] Contrary to the utilization of THF, the use of *t*BuOH as a solvent produced better results. After some experiments under different conditions, we were able to synthesize allene **6** in an acceptable yield of 62 %.



Scheme 2. Synthesis and cyclization of allene **6**.

The cyclization step was performed under typical conditions employing $Pd(OAc)_2/PPh_3$ as catalytic system and K_2CO_3 as a base in DMF as a solvent to afford product **7**, albeit in only 23 %. Therefore, a series of experiments were carried out in order to improve the yield and to optimize the reaction conditions. They were performed with allene **6** and are listed in Table 1. Amongst the solvent used (Entries c–f, Table 1), MeCN was superior, although the yield was still relatively low (38 %; Entry d, Table 1). Replacing $Pd(OAc)_2$ with $Pd(PPh_3)_2Cl_2$ (Entry g, Table 1) did not significantly influence the reaction. A brief study of bases showed that Et_3N (Entry h, Table 1) and Cs_2CO_3 (Entry j, Table 1) were more effective than the initially used K_2CO_3, with Et_3N performing marginally better.

Further study of the cyclization step (presented in Table 2) was mainly focused on the variation of the *N*-substituent, with a few examples possessing a substituted benzene ring. All cyclization substrates were prepared according to the methodology described in Scheme 2. Substrates **8a** and **8b** with larger substituents on the nitrogen atom involved in the bond-forming cyclization step, such as adamantyl or neopentyl motifs (Entries a and b, Table 2), furnished the expected products **9a** and **9b** in 49 % and 56 % yields, respectively. *N*-Substituents, which potentially may interfere with the Pd-promoted reactions, such as allyl and propargyl (compounds **8c**, **8d**, and **8g**; Entries c, d, and g, Table 2), were tolerated, although in some cases the yields were slightly lower.

Since naturally occurring compounds containing indoxyl-derived skeletons (Figure 1) possess an additional substituent attached to the imidazolidinone ring, we next attempted to incorporate this structural feature in the products accessible by the disclosed methodology. For this purpose amino acids were used, and the substituted amide side chain was introduced into the cyclization precursor in several steps as outlined in Scheme 3.

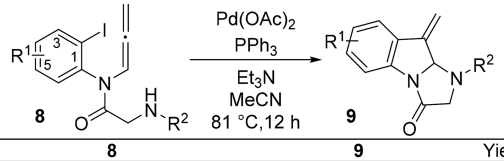
The three-step procedure starting from protected (*S*)-amino acid derivative **10** afforded *N*-propargyl products **11** in good overall yields in all cases. The following isomerization was carried out in THF in the presence of *t*BuOK to afford allene derivatives **12**. The final cyclization step was performed under conditions described above (Table 3). *N*-Unprotected amino acid derivatives **12a**–**c** smoothly formed the condensed structures **13** in acceptable yields as a mixture of *cis*/*trans* isomers.

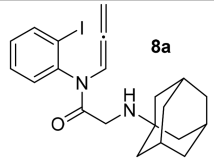
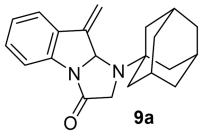
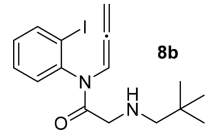
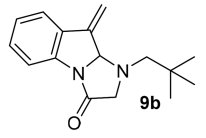
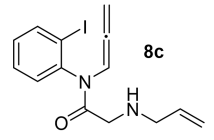
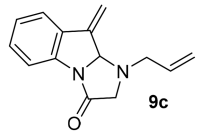
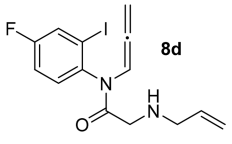
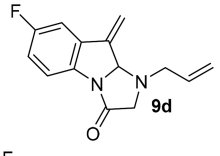
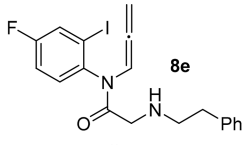
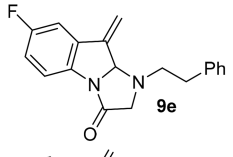
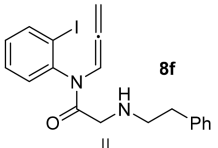
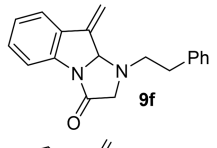
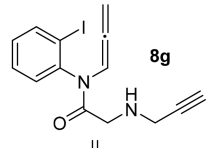
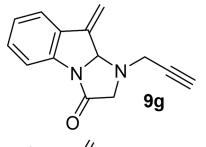
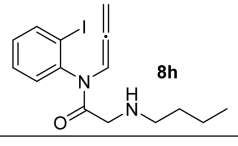
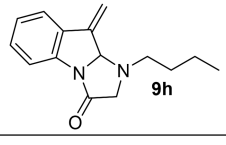
Table 1. Optimization of the reaction conditions for the cyclization step **6** → **7**.[a]

Entry	Pd source	Ligand	Base	Conditions	Time [h]	Yield of **7** [%][b]
a	$Pd(OAc)_2$	PPh_3	K_2CO_3	DMF/95 °C	2.5	23
b	$Pd(OAc)_2$	PPh_3	K_2CO_3	DMF/room temp.	12	27
c	$Pd(OAc)_2$	PPh_3	K_2CO_3	DMF/95 °C	12	23
d	$Pd(OAc)_2$	PPh_3	K_2CO_3	MeCN/81 °C	2.5	38
e	$Pd(OAc)_2$	PPh_3	K_2CO_3	THF/67 °C	12	31
f	$Pd(OAc)_2$	PPh_3	K_2CO_3	dioxane/90 °C	12	23
g	$Pd(PPh_3)_2Cl_2$	–	K_2CO_3	MeCN/81 °C	12	35
h	***$Pd(OAc)_2$***	***PPh_3***	***Et_3N***	***MeCN/81 °C***	***12***	***50***
i	$Pd(OAc)_2$	BINAP	Et_3N	MeCN/81 °C	3	29
j	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	MeCN/81 °C	12	48

[a] Reaction conditions: **6** (0.1 mmol), Pd source (0.01 mmol), ligand (0.02 mmol), base (0.4 mmol), solvent (5 mL). [b] Isolated yields after column chromatography.

Table 2. Study of the cyclization reaction.[a]

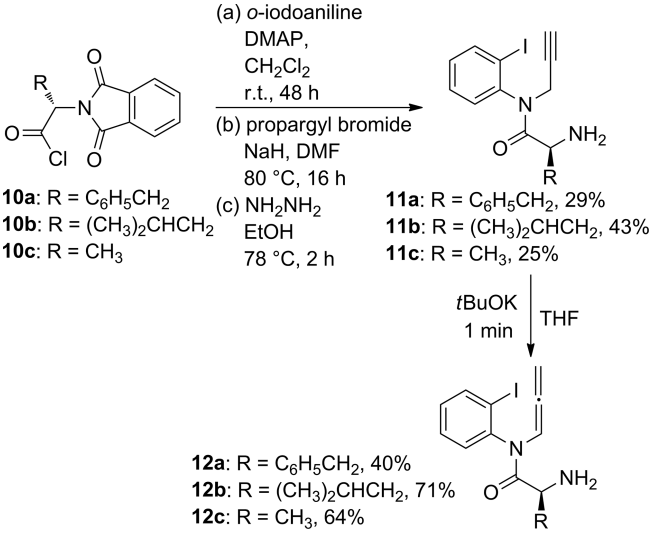


Entry	8	9	Yield [%][b]
a			49
b			56
c			50
d			37
e			55
f			26
g			35
h			35

[a] Reaction conditions: **8** (0.1 mmol), $Pd(OAc)_2$ (0.01 mmol), PPh_3 (0.02 mmol), Et_3N (0.4 mmol), MeCN (5 mL). [b] Isolated yields after column chromatography.

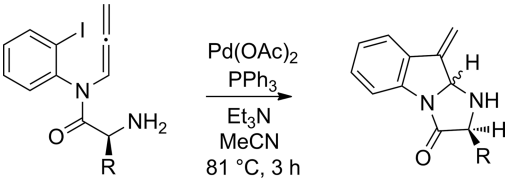
In all cases the major component was the *cis* product, with stereochemical arrangement related to those of naturally occurring substances (Figure 1).

Finally, oxidative transformation of the exocyclic double bond was studied in order to introduce the keto functionality and to create the indoxyl skeleton. Initial ozonolysis was performed on the sulfonamides **14** derived from *cis*-**13** (Scheme 4) to afford indoxyls **15**. Although unstable on silica, these products were isolated in good yields after standard workup (see the Supporting Information).



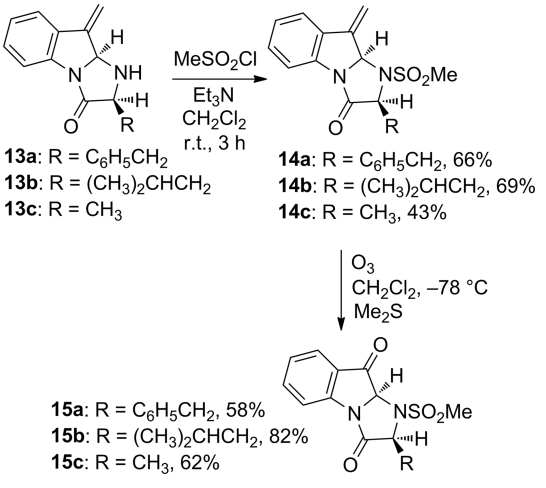
Scheme 3. Synthesis of the amino acid derived allenamides.

Table 3. Cyclization reactions of amino acid derived allenes.[a]



Entry	12	13	*cis*/*trans*	Yield [%][b]
a	**12a**	**13a**, R = $C_6H_5CH_2$	4.2:1[c]	47
b	**12b**	**13b**, R = $(CH_3)_2CHCH_2$	2.1:1[d]	63
c	**12c**	**13c**, CH_3	2.6:1[d]	44

[a] Reaction conditions: **12** (0.5 mmol), $Pd(OAc)_2$ (0.05 mmol), PPh_3 (0.1 mmol), Et_3N (2.0 mmol), MeCN (10 mL). [b] Isolated yields after column chromatography. [c] Separated by column chromatography. [d] Determined by ^1H NMR spectroscopy.



Scheme 4. Synthesis of indoxyl derivatives.

Conclusions

Our exploration of the cyclization processes of allenamides added a novel tactical variant to the synthetic repertoire cen-

tered around these valuable molecules. A cascade sequence secured the consecutive formation of two five-membered rings providing access to indole derivatives. Further oxidation of the exocyclic double bond created an annulated indoxyl skeleton, a structural motif present in many natural products. The indoxyls obtained could be useful starting materials for the preparation of not just some natural products but also their close analogues.

Supporting Information (see footnote on the first page of this article): Experimental procedures and structural data, including ^{1}H and ^{13}C NMR spectra.

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Keywords: Indoxyl · Allenamide · Palladium · Cyclization · Annulation · Heterocycles

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