Cyclizations of Allenenes

Palladium(0)-Catalyzed Tandem Cyclization of Allenenes**

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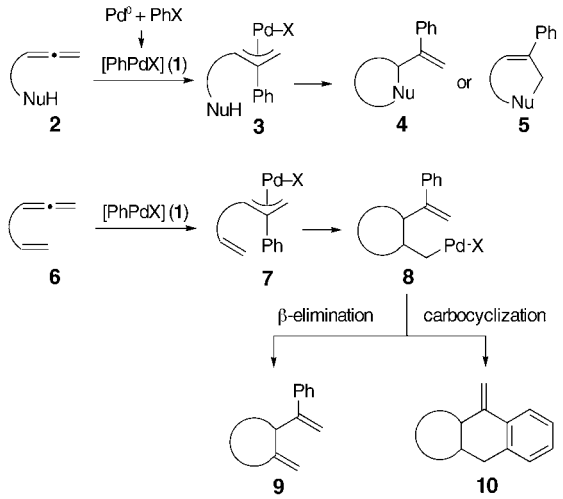
Allenes have become more versatile intermediates in organic synthesis as a result of recent developments in transition-metal-catalyzed reactions.[1,2] In particular, allenes of general type **2**, which bear a nucleophilic moiety such as a nitrogen- or oxygen-containing functional group, are a well-known class of compounds that undergo a variety of palladium(0)-catalyzed cyclizations to form cyclic products **4** or **5** (Scheme 1).[3]



Scheme 1. Palladium-catalyzed cyclization of allenes.

Recent studies in this area revealed that three-[4] or four-membered heterocycles[5] could also be synthesized efficiently by the palladium-catalyzed cyclization of allenes **2**. In sharp contrast, however, palladium-catalyzed reactions of allenes that contain an additional multiple bond have scarcely been studied.

In analogy to the reactions of allenes **2**, which terminate with the intramolecular reaction of the π-allyl palladium intermediate with a nucleophile, the allenene **6** could undergo a tandem cyclization of the type shown in Scheme 1 under

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[**] We thank Dr. S. Aoki, Graduate School of Pharmaceutical Sciences, Osaka University, for NMR analyses. This work was supported by a Sasakawa Scientific Research Grant from the Japan Science Society.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

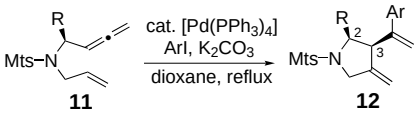
 DOI: 10.1002/ange.200351011 © 2003 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

similar conditions. Thus, the π-allyl palladium(II) intermediate **7**, formed by the reaction of the allenene **6** with the phenyl palladium(II) halide **1**, would be converted into the intermediate **8** by carbocyclization.[6] If β-hydride elimination then predominated, a monocyclic product **9** would be produced. However, further carbocyclization onto the aromatic ring[7] would lead to a tricyclic product such as **10** in a single step. Suppression of both β-hydride elimination in **8** and the potential Heck-type reaction between the aryl halide and the vinyl group in **6** would be required for a tandem cyclization to take place.

Recently, some palladium-catalyzed carbocyclization reactions of bisallenes,[8] allenynes,[9] and allenenes[10] were reported.[11] However, as far as we are aware there has been no report of a palladium(0)-catalyzed tandem cyclization of an allene that contains an additional multiple bond.[12] Herein we report the first palladium(0)-catalyzed tandem carbocyclization of allenenes for the synthesis of tri- and tetracyclic nitrogen heterocycles.

With a view to synthesizing a variety of nitrogen heterocycles, we prepared the substrates **11a–c** through the diethylzinc-mediated reductive synthesis of amino allenes catalyzed by palladium(0),[13] followed by *N*-allylation. In an initial experiment, we found that the carbocyclization of allenenes and subsequent β-hydride elimination proceeded efficiently upon treatment with iodobenzene and potassium carbonate in the presence of a catalytic amount of $[Pd(PPh_3)_4]$ (Table 1). The reaction of **11a** in refluxing dioxane provided the 2,3-*cis*-pyrrolidine **12a** in 60% yield as the only isolable product (Table 1, entry 1).[14] The use of other solvents, such as MeCN, DMF, or DMSO, resulted in lower yields. Whereas the use of 4-iodoanisole and 4-iodotoluene as the aryl halide gave comparable results (Table 1, entries 2 and 3), only 36% of the pyrrolidine **12d** was obtained when the reaction was carried out with the electron-poor 1-iodo-4-nitrobenzene (Table 1, entry 4). Furthermore, the substituent α to the allene was found to be extremely important for the efficiency of the cyclization. Thus, the allenenes **11b** and **11c**, which have an effectively smaller α substituent than **11a** (R = Bn and *i*Bu, respectively) required prolonged reaction times for the complete consumption of the starting materials (Table 1, entries 5 and 6). Moreover, no cyclized product was isolated when the corresponding unsubstituted allenene (R = H) was used.[15] We speculate that the bulky α substituent stabilizes the conformation required for the carbocyclization.

Table 1: Stereoselective synthesis of 2,3-*cis*-pyrrolidines **12** by the palladium(0)-catalyzed carbocyclization of allenenes **11**.[a]

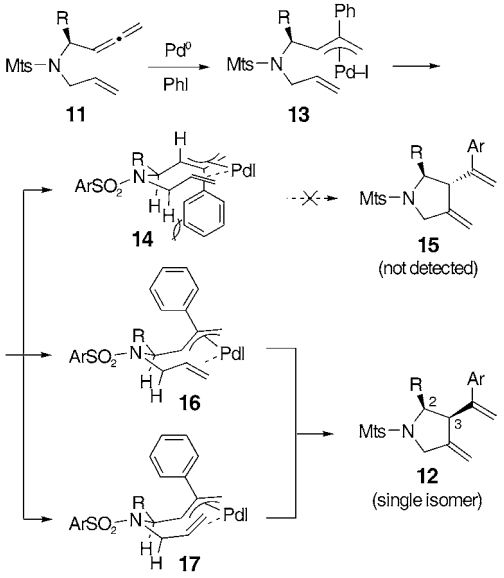


11 **12**

Entry	Allenene	R	ArI	*t* [h]	Product	Yield [%][b]
1	**11a**	*i*Pr	PhI	4.5	**12a**	60
2	**11a**	*i*Pr	4-MeOPhI	3	**12b**	60
3	**11a**	*i*Pr	4-MePhI	8	**12c**	56
4	**11a**	*i*Pr	4-NO_2PhI	11	**12d**	36
5	**11b**	Bn	PhI	24	**12e**	58
6[c]	**11c**	*i*Bu	PhI	24	**12f**	46

[a] Reactions were carried out in the presence of $[Pd(PPh_3)_4]$ (10 mol%), ArI (2 equiv), and K_2CO_3 (2 equiv) in dioxane under reflux. [b] Yields of isolated products. The 2,3-*trans* products were not observed (2,3-*cis*/*trans* > 98:2). [c] Increased amounts of ArI (4 equiv) and K_2CO_3 (4 equiv) were used. Mts = 2,4,6-trimethylphenylsulfonyl.

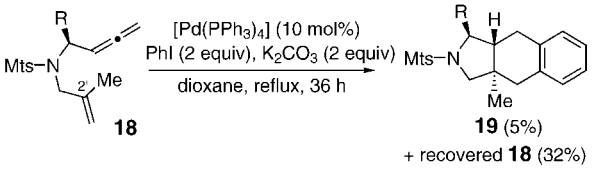
The observed 2,3-*cis* selectivity in the pyrrolidine formation can be rationalized as shown in Scheme 2. If a π-allyl palladium(II) intermediate **13** underwent carbocyclization via the conformation **14**, the 2,3-*trans*-pyrrolidine **15** would be obtained. However, an unfavorable steric interaction between the pseudoaxial hydrogen atoms and the phenyl group in **14** destabilizes this conformer. Thus, ring formation proceeds preferentially via the more abundant conformers **16** and/or **17** to yield the *cis*-pyrrolidine **12** as a single isomer.



Scheme 2. Stereoselective formation of 2,3-*cis*-pyrrolidines **12**.

Next, we investigated inhibition of the β-hydride elimination to promote the desired tandem cyclization. We expected that the replacement of the β-hydrogen atom with an alkyl group would suppress the β-hydride elimination and allow another carbopalladation step. However, the introduction of a methyl group at the 2′-position dramatically decreased the reactivity of the allenene, and the desired tricyclic product **19** was obtained from the 2′-methylated allenene **18** in just 5% yield after 36 h (Scheme 3).

We then anticipated that the introduction of a substituent at the olefin terminus (3′-position) would impede the required arrangement of the palladium center relative to the hydrogen



Scheme 3. Reaction of the 2′-methylated allenene **18**.

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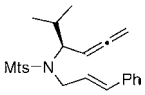
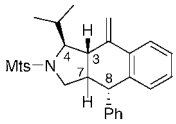
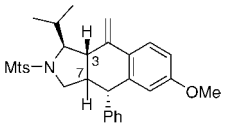
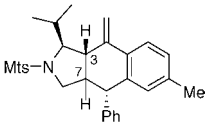
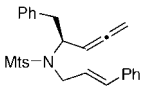
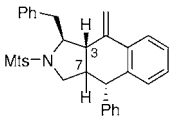
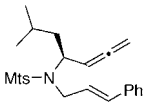
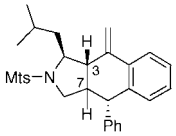
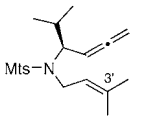
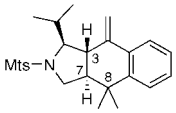
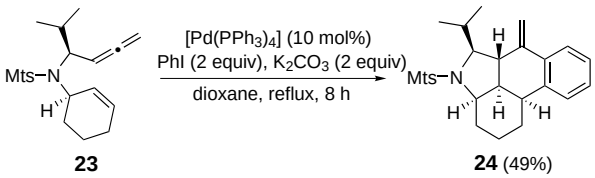
atom for β-hydride elimination to occur.[16,17] Fortunately, we found that the *N*-(*E*)-cinnamyl derivative **20a** reacted to give a separable mixture of the benzoisoindole derivatives **21a** and **22a** in moderate yields (41 and 10%, respectively) upon treatment with a catalytic amount of palladium(0), iodobenzene, and potassium carbonate in dioxane (Table 2, entry 1). These cyclized products were characterized by ^{1}H NMR, ^{13}C NMR, NOE, and COSY spectroscopic analysis, and the structure of **21a** was also confirmed by HMQC and HMBC analysis. This is the first example of a palladium(0)-catalyzed tandem cyclization of allenenes. 4-Iodoanisole and 4-iodotoluene could also be used for this transformation (Table 2, entries 2 and 3). The *N*-cinnamylamino allenes **20b** and **20c**, in which the α substituent is effectively smaller, also reacted to afford the expected tricyclic products, although prolonged reaction times were required (23–29 h). An improvement of the yields of the desired cyclized products was hampered by the formation of unidentified by-products. Substituents other than a phenyl group at the olefin terminus can also promote the tandem cyclization. Thus, the reaction of the *N*-(3,3-dimethylallyl)amino derivative **20d** yielded the expected cyclized product **21f** with geminal dimethyl substitution at C8 in a stereoselective manner. In all the cases listed in Table 2 the stereoselectivity of the first cyclization (which dictates the relative configuration at C3 and C4 in the product) was opposite to that observed in the formation of the pyrrolidines (Table 1).[14] Furthermore, although the stereoselectivities at C7 were not very high, the configurations of the other two stereocenters (C3 and C8) created in the reaction were controlled completely. We assume that the steric bulk of the cinnamyl group interferes in the first cyclization to hinder the formation of the 3,7-*cis* product.

Table 2: Palladium(0)-catalyzed tandem cyclization of allenenes **20**.[a]

Entry	Substrate	ArI	*t* [h]	Product	Yield [%][b]
1		PhI	7.5		
	20a			**21a** (3,7-*trans*)	41
				22a (3,7-*cis*)	10
2	**20a**	4-MeOPhI	3.5		
				21b (3,7-*trans*)	43
				22b (3,7-*cis*)	20
3	**20a**	4-MePhI	7		
				21c (3,7-*trans*)	37
				22c (3,7-*cis*)	18
4		PhI	23		
	20b			**21d** (3,7-*trans*)	30
				22d (3,7-*cis*)	24
5		PhI	29		
	20c			**21e** (3,7-*trans*)	25
				22e (3,7-*cis*)	17
6		PhI	28		
	20d			**21f**	42

[a] Reactions were carried out in the presence of $[Pd(PPh_3)_4]$ (10 mol%), ArI (2 equiv), and K_2CO_3 (2 equiv) in dioxane under reflux. [b] Yields of isolated products.

Finally, we investigated the reaction of the *N*-cyclohexenyl derivative **23** (Scheme 4). Exposure of **23** to the standard cyclization conditions led to the formation of the desired tetracyclic compound **24** as a single isomer. The structure of **24** was confirmed by NMR analysis, including NOE and COSY experiments. This result clearly indicates the utility of our tandem cyclization as a novel method for the synthesis of complex heterocycles.



23 **24** (49%)

Scheme 4. Synthesis of the tetracyclic compound **24**.

In conclusion, we have developed a novel tandem cyclization of allenenes for the synthesis of tri- and tetracyclic nitrogen heterocycles. This study demonstrated that allenes

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with an additional multiple bond can undergo a tandem cyclization in the presence of a palladium(0) catalyst and an aryl iodide and that complex heterocyclic skeletons can be constructed from readily prepared allenenes. Further investigations to improve the yields of the reactions and our understanding of the observed stereoselectivity are in progress in our laboratory, as well as the synthesis of other hetero- and carbocycles by this method.

Received: January 23, 2003 [Z51011]

Keywords: allenes · cyclization · domino reactions · heterocycles · palladium

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