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Novel Synthesis of 3-Azabicyclo[3.1.0]hexanes by Unusual Palladium(0)-Catalyzed Cyclopropanation of Allenenes

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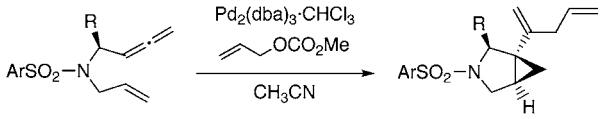
ABSTRACT



Novel stereoselective synthesis of 3-azabicyclo[3.1.0]hexanes from allenenes is presented. Treatment of N-protected 4-alkyl-4-(*N*-allyl)amino allenes with allyl carbonate and a catalytic amount of $Pd_2(dba)_3$·$CHCl_3$ in MeCN leads to stereoselective formation of the 3-azabicyclo[3.1.0]-hexane framework in moderate to good yields.

3-Azabicyclo[3.1.0]hexane is a basic structure of biologically active natural products such as CC-1065,[1] duocarmycin,[1] and indolizomycin,[2] and also a framework of a pharmacologically important class of compounds such as 3,4-methanoprolines,[3] poly-L-proline type II peptide mimetics,[4] and conformationally rigid analogues of [1,4′-bipiperidine]-4′-carboxamides.[5] Moreover, heterocyclic compounds with this ring system are known as useful intermediates for cyclopropane amino acids such as conformationally restricted analogues of L-glutamate[6] and γ-aminobutyric acid (GABA).[7] Therefore, stereoselective construction of a nonracemic 3-azabicyclo[3.1.0]hexane framework is an attractive research subject for organic chemists. Although this bicyclic skeleton can be constructed via titanium-mediated cyclization,[8] cyclopropanation with sulfur ylide,[9] metal-mediated radical cyclization,[10] and reaction of metal carbene complexes,[11] catalytic synthesis of 3-azabicyclo[3.1.0]hexanes is relatively rare.[12,13]

In connection with our studies directed toward palladium(0)-catalyzed cyclization of allenes,[14,15] we recently reported that tricyclic heterocycles **3** were formed through the tandem cyclization of allenenes **1** upon treatment with aryl iodide,

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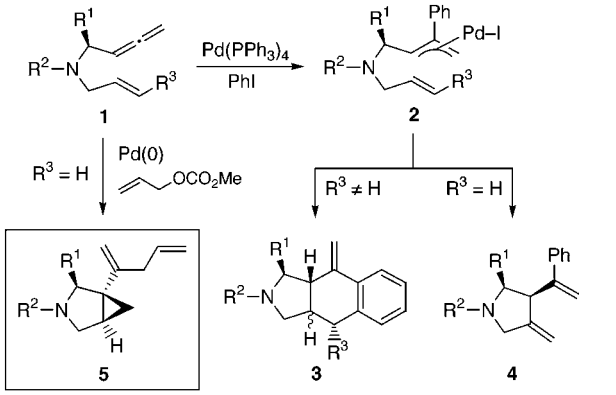
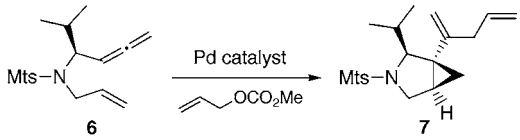
Scheme 1



potassium carbonate, and catalytic $Pd(PPh_3)_4$ (Scheme 1).[15b] Interestingly, the reactivity of the palladium(II) intermediates **2** could be controlled by substitution (R^3) at the olefin terminus: allenes having a terminal olefin ($R^3 = H$) led to exclusive formation of 2,3-*cis*-pyrrolidines **4**. During the course of this study, we found that 3-azabicyclo[3.1.0]-hexanes **5** can be directly constructed from allenenes by simply changing the reaction conditions. Although the formation of small rings, including cyclopropanes,[16] by intramolecular nucleophilic attack onto the allenic moiety is well documented,[14,17] direct synthesis of bicyclic cyclopropanes by the reaction of allenes with an additional multiple bond is unprecedented.[18] In this communication, we present the first palladium(0)-catalyzed highly stereoselective cyclopropanation of allenenes to form nonracemic 3-azabicyclo[3.1.0]hexanes.

The requisite allenenes were synthesized through the diethylzinc-mediated reductive synthesis of amino allenes catalyzed by palladium(0),[19] followed by N-allylation. First, we investigated reaction of allenene **6** under some palladium-catalyzed cyclization conditions (Table 1). We found that

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst (10 mol %)	solvent	temp (°C)	time (h)	yield[b]
1	$Pd(PPh_3)_4$	dioxane	100	4	16%
2	$Pd(PPh_3)_4$	CH_3CN	80	12	0%
3	$[(\eta^3\text{-}C_3H_5)PdCl]_2$	CH_3CN	80	7	0%
4	$Pd_2(dba)_3{\cdot}CHCl_3$	CH_3CN	80	4	20%
5[c]	$Pd_2(dba)_3{\cdot}CHCl_3$	CH_3CN	80	5	64%
6[c]	$Pd_2(dba)_3{\cdot}CHCl_3$	dioxane	80	12	0%

[a] Unless otherwise stated, reactions were carried out with a palladium catalyst (10 mol %) and allyl carbonate (2 equiv). [b] Yields of isolated products. [c] Increased amount of allyl carbonate (6 equiv) was used. Abbreviation: Mts = 2,4,6-trimethylphenylsulfonyl.

treatment of the allenene **6** with allyl carbonate in the presence of a catalytic amount of $Pd(PPh_3)_4$ in dioxane at 100 °C, which are similar reaction conditions to those for the tandem cyclization of allenenes with an aryl iodide,[15b] afforded 3-azabicyclo[3.1.0]hexane **7** in 16% yield, along with a number of unidentified products (entry 1). Although the reaction of **6** with catalytic $Pd(PPh_3)_4$ or $[(\eta^3\text{-}C_3H_5)PdCl]_2$ in CH_3CN led to recovery of the starting allenene (entries 2 and 3), a slightly improved result (20% yield) was obtained when using $Pd_2(dba)_3{\cdot}CHCl_3$ as a catalyst (entry 4). In this case, a considerable amount of **6** was recovered. However, increased loading of allyl carbonate (6 equiv) improved the yield to 64% (entry 5), and no starting material was recovered. In all cases, cyclized product of the type **4** (Scheme 1) was not isolated, and the cyclopropanation reaction proceeded in a stereoselective manner.[20]

Having established the reaction conditions affording the desired cyclopropane **7**, we next investigated the reaction

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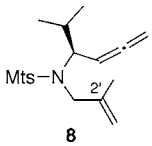
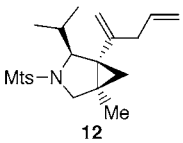
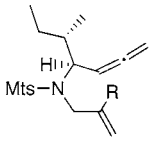
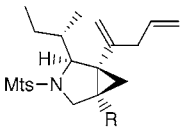
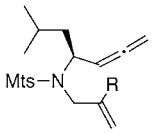
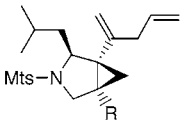
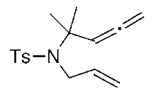
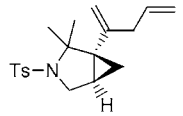
(20) Confirmation of the stereochemistry of the cyclized product **7** was based on NOE analysis.

Table 2. Synthesis of 3-Azabicyclo[3.1.0]hexanes from Allenenes[a]

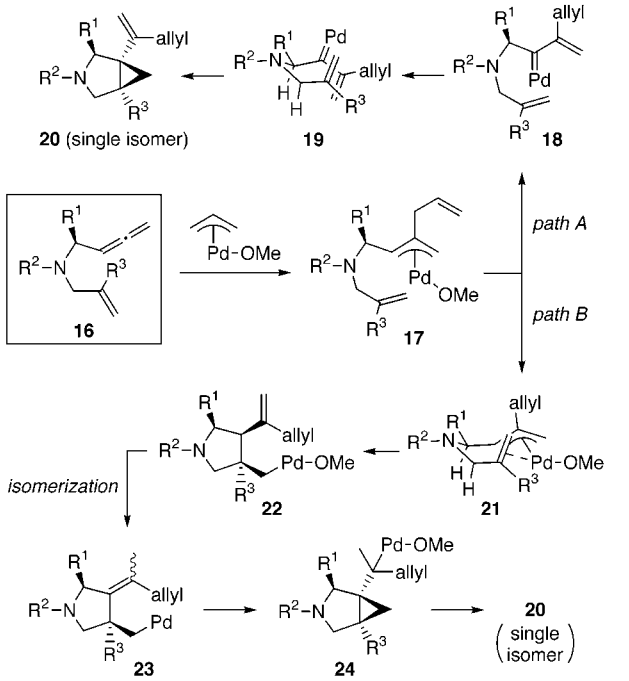
entry	allenene	time	product	yield[b]
1	 **8**	7 h	 **12**	59%
2	 **9a** (R = H)	7 h	 **13a** (R = H)	57%
3	**9b** (R = Me)	24 h	**13b** (R = Me)	39%
4	 **10a** (R = H)	24 h	 **14a** (R = H)	35%
5	**10b** (R = Me)	24 h	**14b** (R = Me)	36%
6	 **11**	60 h	 **15**	24%[c]

[a] All reactions were carried out with $Pd_2(dba)_3 \cdot CHCl_3$ (10 mol %) and allyl carbonate (6 equiv) in CH_3CN. [b] Yields of isolated products. [c] Starting allenene **11** was recovered (29%).

of allenenes **8**−**11** (Table 2). The treatment of allenene **8** having a methyl group on the 2′-position with allyl carbonate and catalytic $Pd_2(dba)_3 \cdot CHCl_3$ in CH_3CN at 80 °C stereoselectively gave **12** having two quaternary carbons in 59% yield. Similarly, both of the isoleucine derivatives, **9a** and **9b**, which bear a *sec*-butyl group on the α-position, afforded 3-azabicyclo[3.1.0]hexane **13a** and **13b** in 57 and 39% yields, respectively, under identical reaction conditions. In contrast, allenenes **10a** and **10b** having an isobutyl group (entries 4 and 5) and **11** having a geminal dimethyl group (entry 6) gave relatively low yields of the bicyclic cyclopropanes **14a**, **14b**, and **15**, respectively. In the reaction of **11**, 29% of the starting material was recovered after a prolonged reaction time (60 h). These results clearly show that the presence of an appropriate sterically congested substituent at the α-position to the allenic moiety, which would assist and not interfere in the cyclization, is extremely important for the successful conversion. In fact, the corresponding allenene without the α-substituent was completely inert to the reaction conditions. In some cases, isolation of the desired bicyclic cyclopropane from other unidentified products was troublesome. We obtained pure cyclized products by flash chromatography, followed by recrystallization or preparative TLC.

Although the reaction mechanism of this cyclopropanation is not understood, this reaction clearly demonstrates a novel

Scheme 2



reactivity of allenes with a palladium(0) catalyst. Scheme 2 shows two explanations of the reaction leading to the bicyclic cyclopropanes **20**. Reaction of allenene **16** with π-allylpalladium(II) methoxide, derived from allyl carbonate and palladium(0), gives the allylated π-allylpalladium(II) intermediate **17**. If deprotonation of **17** predominates to form a palladium carbene intermediate **18** (path A), stereoselective formation of the cyclopropane **20** is readily understood.[21] However, to the best of our knowledge, generation of a palladium carbene species from π-allylpalladium(II) methoxide is unprecedented. If the intramolecular carbopalladation of **17** via **21** predominates (path B), alkylpalladium intermediate **22** would be formed.[22] Although isomerization of the double bond of **22** to **23** is necessary, this pathway also enables the stereoselective formation of bicyclic cyclopropane **20**. Path A better explains the experimental result that a cyclized product of the type **4** (Scheme 1) is not observed in the reaction mixture; however, further investigation would be necessary to determine the reaction mechanism. The reason the present reaction conditions promote the cyclopropanation reaction instead of the Oppolzer cyclization leading to **4** is unclear.

In conclusion, we have developed a palladium(0)-catalyzed stereoselective cyclopropanation of allenenes to form 3-azabicyclo[3.1.0]hexanes in moderate to good yields. Further studies in the field of allenene cyclization and

(21) For a review on the cyclopropanation of palladium carbenes, see: Reiser, O. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Eds.; John Wiley & Sons: New York, 2002; Vol. 1, pp 1561−1577.

(22) From our previous study on the palladium-catalyzed cyclization of allenenes leading to pyrrolidine **4** (Scheme 1),[15b] the cis cyclization to give **22** (Scheme 2) would be the predominant process over the trans cyclization.

conversion of the bicyclic cyclopropanes into biologically important compounds are currently under investigation.

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Supporting Information Available: Representative experimental procedures, as well as ^{1}H NMR spectra for all the cyclized products. This material is available free of charge via the Internet at http://pubs.acs.org.

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