Pergamon

Tetrahedron Letters 40 (1999) 7393–7397

TETRAHEDRON LETTERS

Palladium-catalyzed regio- and stereoselective synthesis of *N*-protected 2,4-dialkylated azacyclobutanes from amino allenes

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Received 15 July 1999; accepted 5 August 1999

Abstract

Palladium-catalyzed reaction of *N*-arylsulfonyl-1-alkyl-3,4-dienylamines with an aryl iodide in the presence of potassium carbonate in DMF at around 70°C affords most predominantly the 2,4-*cis*-disubstituted azacyclobutanes bearing an aryl group on the double bond in good yields.

The transition metal-catalyzed ring formation of amino- and hydroxy-allenes in a highly regio- and stereoselective manner has attracted much attention in recent years.[1] Allenes bearing a protected or unprotected amino group separated from the carbon atom of the allene moiety by one to four carbon atoms have been attractive substrates for constructing azacycles.[2–5] Various transition-metal complexes such as mercury(II),[2] palladium(0 or II),[3] silver(I),[4] and organolanthanides[5] have been reported to be effective catalysts for the cyclization reaction.[6]

Although the cyclization reactions of various amino allenes by transition metals to yield either five- and/or six-membered azacycles have been well-documented, ring-closure yielding three- or four-membered azacycles from amino allenes has had no precedent until quite recently.[7,8] We reported very recently for the first time that the aziridination reaction proceeded efficiently when a dioxane solution of certain allenic sulfonamides, iodobenzene, potassium carbonate, and a catalytic amount of $Pd(PPh_3)_4$ was refluxed, affording the corresponding aziridines in good yields.[7]

As part of our studies of transition metal-catalyzed cyclization reactions of amino allenes, we studied the palladium-catalyzed azacyclobutane forming reaction from amino allenes. It was our expectation to be able to synthesize *N*-protected azacyclobutanes **2** from an amino allene **1** by exposure to a mixture of a catalytic amount of Pd(0), an aryl halide, and a base. In principle, the reaction of amino allenes under ordinary conditions could afford one, or a mixture, of four possible products **2**, **3**, **4** and **5**. Thus, it is not an easy matter to predict whether **a**, **b**, **c** or **d** would be the major reaction pathway (Scheme 1).[3e,f,9] While this work was in progress, although only an isolated example, an independent report by Kang

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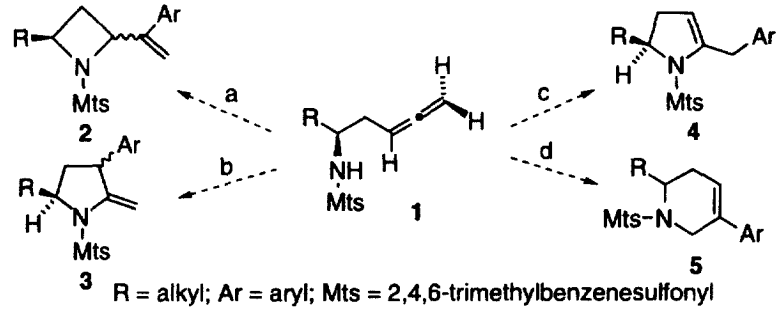
0040-4039/99/$ - see front matter
PII: S0040-4039(99)01517-8

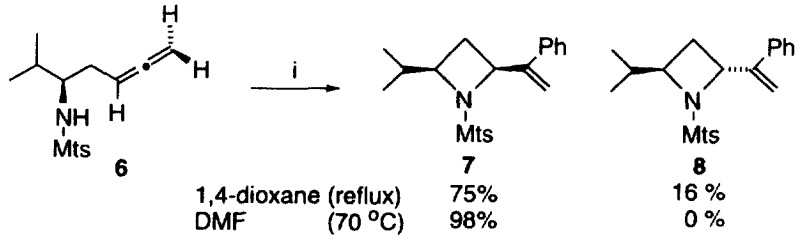
and co-workers appeared.[8] Thus, the palladium-catalyzed cyclization of a *N*-protected amino allene with hypervalent iodonium salts was reported to yield a mixture of four- and six-membered azacycles. The publication prompted us to report our independent results obtained under different conditions at this time.



Scheme 1.

Initial attempts at the palladium-catalyzed azacyclobutane cyclization reaction on certain *N*-*tert*-butoxycarbonylamino (*N*-Boc) allene were unsuccessful. Either the starting material was recovered or multiple unidentified compounds were produced under forced conditions. Fortunately, use of an arylsulfonyl *N*-protective group on the amino group overcame the problem. Consequently, all the requisite enantiopure amino allenes **6**, **9** and **10**, and **11** and **12** bearing an arylsulfonyl *N*-protective group were prepared in acceptable yields from (*S*)-valinol, (*S*)-leucinol, and (*S*)-phenylalaninol, respectively, according to the usual method.[3f,10] From an experimental point of view, the *N*-arylsulfonyl compounds **6** and **9**–**12** have the advantage in that they are usually stable.

To determine the viability of the cyclization reaction of amino allenes, we initially examined the cyclization reaction of the amino allene **6** by using 10 mol% of $Pd(PPh_3)_4$ in 1,4-dioxane under reflux for 2 h in the presence of iodobenzene and K_2CO_3 (Scheme 2).[7,11] The desired azacyclobutane derivative **7** (75% yield) was obtained along with the stereoisomer **8** (16% yield). Arylation takes place at the allenic central carbon atom. Fortunately an attempted cyclization of the amino allene **6** under otherwise identical reaction conditions in DMF resulted in the exclusive formation of 2,4-*cis*-azacyclobutane **7** in 98% yield. While we cannot conclusively rule out the presence of a trace quantity of the 2,4-*trans*-isomer **8**, the 2,4-*cis* isomer **7** was the only one detected.



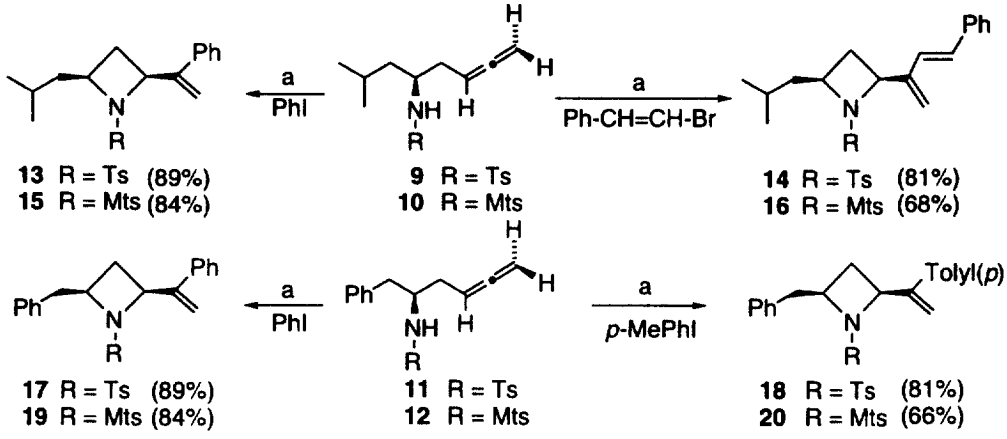
Scheme 2. Reagents and condition: (i) $Pd(PPh_3)_4$ (10 mol%), K_2CO_3 (4 equiv.), PhI (4 equiv.), reflux or 70°C; 2 h

Previously, we reported that 1,4-dioxane was the solvent of choice for the regio- and stereoselective aziridination reaction of certain amino allenes.[7] Although its exact role is not clear, DMF is a more suitable solvent for the present 2,4-*cis*-selective azacyclobutane cyclization reaction.

The structure and stereochemistry assigned for azetidines **7** and **8** rested strongly on NMR (NOESY, ^1H–^1H COSY, GHMBC) spectral analyses.

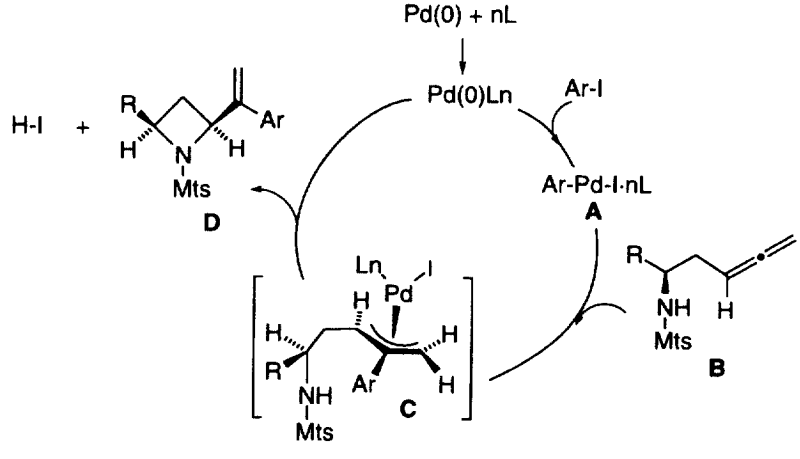
As shown in Scheme 3, quite similar results were obtained by exposure of other chiral amino allenes **9**–**12** to 10 mol% of $Pd(PPh_3)_4$ in the presence of an appropriate aryl or alkenyl halide and

K_2CO_3 in DMF, giving the corresponding 2,4-*cis*-disubstituted azacyclobutanes in good to high yields. Recently, Hiemstra, Rutjes, and co-workers have reported that allenes bearing an amino functionality (as a cyclic amide) separated from the carbon atom of the allene moiety by two carbon atoms affords the corresponding five-membered azacycles.[3e,f] In sharp contrast, in all our cases examined, there was no evidence of the formation of any five- or six-membered azacyclic compound.



Scheme 3. Reagents and condition: (a) $Pd(PPh_3)_4$ (10 mol%); K_2CO_3 (4 equiv.); aryl or alkenyl halide (4 equiv.); in DMF 70°C; 0.5–2 h

Although the origin of regio- and stereoselectivity in the cyclization reaction is unclear, a plausible rationale for the intramolecular azacyclobutane cyclization reaction of an amino allene **B** is depicted in Scheme 4.[12] The arylpalladium(II) iodide **A**, formed in situ from an aryl halide and Pd(0), would generate a η^3-allylpalladium complex **C** by reaction with an amino allene **B**. The η^3-allylpalladium moiety in **C** would be sufficiently electrophilic to undergo nucleophilic attack by the nitrogen, affording the 2,4-*cis*-2,4-disubstituted azacyclobutane **D**.



Scheme 4.

In summary, the palladium-catalyzed reaction proceeds in a regio- and stereoselective manner providing most predominantly the 2,4-*cis*-disubstituted azacyclobutanes in good yields. The described procedure provides a reliable and efficient methodology for the intramolecular cyclization of *N*-protected amino allenes into the corresponding alkenylazetidines bearing an aryl group on the double bond. We are

now undertaking extensive study toward clarification of the scope of the present reaction under various reaction conditions.[13]

The following procedure for the synthesis of azacyclobutane **7** from the *N*-protected amino allene **6** is representative. To a stirred mixture of the allene **6** (50 mg, 0.16 mmol), $Pd(PPh_3)_4$ (18.5 mg, 10 mol%), and K_2CO_3 (88 mg, 4 equiv.) in 0.5 mL of DMF was added dropwise a solution of iodobenzene (71.6 μL, 4 equiv.) in DMF (1 mL) and the whole mixture was heated at 70°C with stirring under argon for 2 h. It was then cooled to room temperature and water (5 mL) was added. The mixture was extracted with ether. The extract was washed with brine and dried over $MgSO_4$. The usual workup followed by flash chromatography over silica gel with *n*-hexane:AcOEt (10:1) gave 61 mg (98% yield) of the azetidine **7**: colorless crystals from hexane; mp 75°C. $[\alpha]^{25}_D$ −14.04 (*c* 0.285, $CHCl_3$).

Acknowledgements

This work was supported by Japan Health Sciences Foundation and Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan. H.O. is grateful to Research Fellowships from the Japan Society for the Promotion of Science for Young Scientists.

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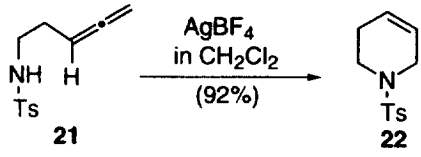
13. Transition metal-assisted cyclization of amino allenes affording six-membered azacycles has been extensively studied. In fact, silver(I)-catalyzed cyclization reaction of amino allene **21** leads exclusively to the six-membered azacycle **22** in 92% isolated yield. Details will be reported in a full paper.



21 **22**