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PALLADIUM-CATALYZED *CIS*- AND *TRANS*-ANNULATIONS TO 1,3-CYCLOHEXADIENE AND 1,3-CYCLOHEPTADIENE[1]

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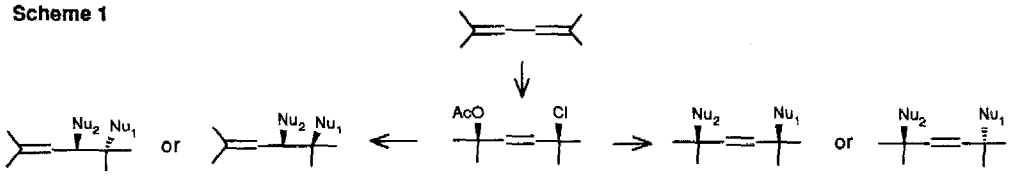
Summary: A method for *cis*- and *trans*-annulations to 1,3-cycloalkadienes was developed, which is based on a palladium-catalyzed 1,4-chloroacetoxylation and subsequent stereocontrolled nucleophilic substitution of the chloro and acetoxy groups.

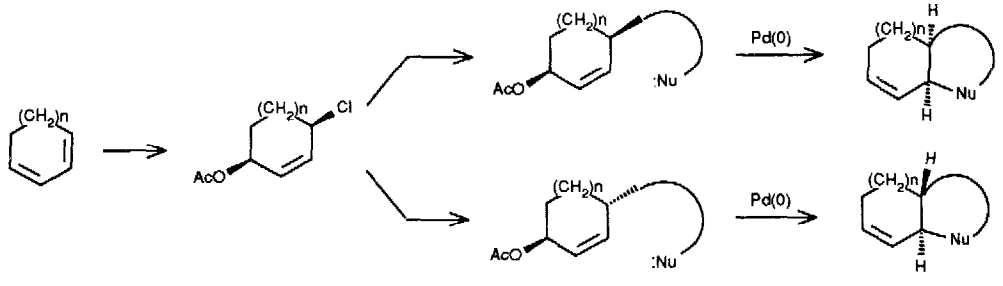
We have recently developed methodology for the addition of nucleophiles to conjugated dienes,[2-4] which is based on the palladium-catalyzed 1,4-chloroacetoxylation and subsequent stereocontrolled substitution of the chloro and acetoxy groups (Scheme 1). The approach allows full control of the 1,4-relative stereochemistry in both cyclic and acyclic systems. Furthermore, the metal-catalyzed nucleophilic substitution of the leaving groups (AcO^- and Cl^-) can be directed towards γ-substitution (S_N2'), leading to useful 1,2-functionalizations.[3g,4c,5]

Scheme 1



Annulation reactions of rings leading to fused-ring systems constitute a useful type of reaction in organic synthesis.[6] An important aspect of such annulations is the control of stereochemistry at the bridgehead carbons. For example, Robinson annulation with subsequent reduction, normally leads to the *trans*-fused rings. We have been engaged for some time in a project with the aim of developing *cis*- and *trans*-annulations to 1,3-cycloalkadienes using the chloroacetoxylation approach. The principle is shown in Scheme 2. In this communication we report our results obtained so far on these stereocontrolled annulation reactions.[1,7]

Scheme 2

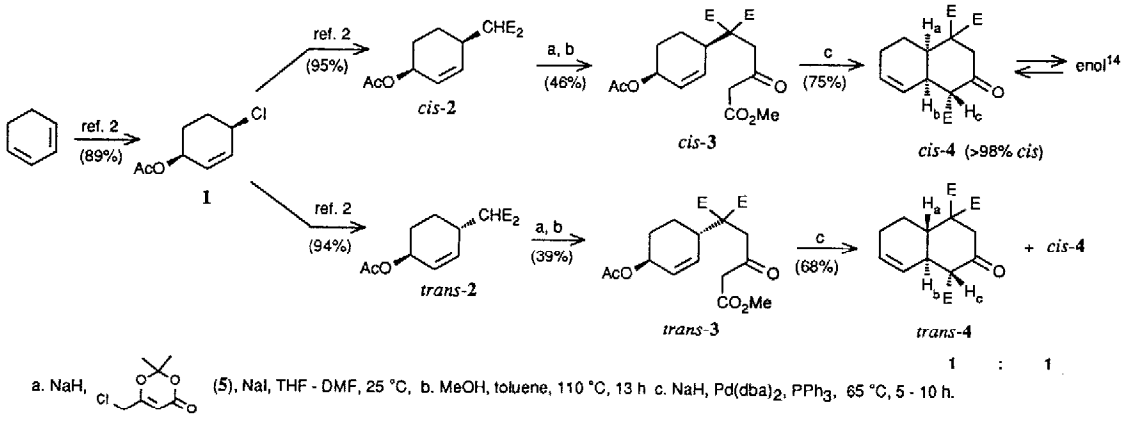


In the approach according to Scheme 2 we first tried to use non-stabilized enolates as nucleophiles in the palladium-catalyzed cyclization step.[8] It has been reported in the literature that intermolecular palladium-catalyzed alkylations of allylic acetates with non-stabilized enolates proceed under mild conditions and with retention of configuration.[9] Since we were not able to obtain the desired cyclizations with non-stabilized enolates[8] we turned our attention to their stabilized counterparts. The use of stabilized enolates in palladium-

catalyzed substitution of allylic acetates, including cyclizations, is well documented in the literature.[10,11]

1,4-Functionalizations of 1,3-cyclohexadiene to *cis*- and *trans*-**2** were done according to ref. 2. The acetoacetate chain was introduced using the Boeckman β-keto ester cation equivalent, 6-chloromethyl-2,2-dimethyl-1,3-dioxen-4-one (**5**),[12] followed by thermolysis in the presence of methanol (Scheme 3).

Scheme 3 (E = CO_2Me)

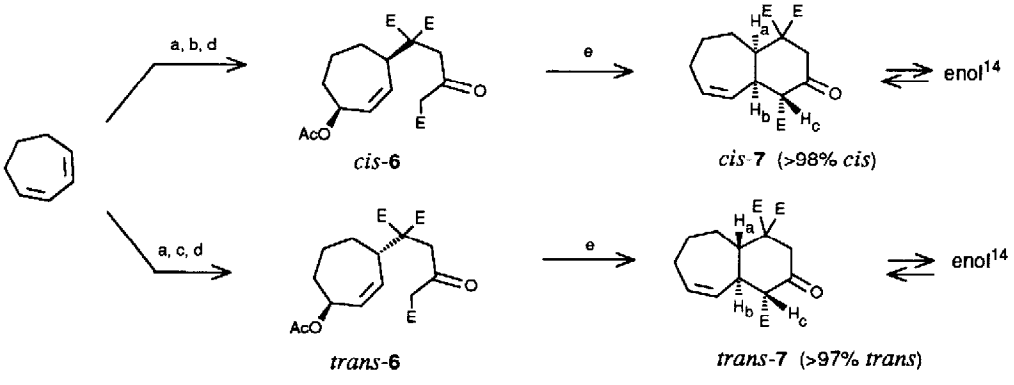


a. NaH, (**5**), NaI, THF - DMF, 25 °C, b. MeOH, toluene, 110 °C, 13 h c. NaH, $Pd(dba)_2$, PPh_3, 65 °C, 5 - 10 h.

Palladium-catalyzed cyclization of *cis*- and *trans*-**3**, thus obtained, was accomplished by using $Pd(dba)_2$[13] (dba = dibenzylideneacetone) in the presence of triphenylphosphine as the catalyst, which generates a Pd(0)phosphine complex *in situ*. The cyclization of *cis*-**3** was highly stereospecific and afforded *cis*-**4**, which was found to be in an equilibrium with its enol form.[14] The corresponding cyclization of *trans*-**3** was not stereospecific and gave the expected product *trans*-**4** and *cis*-**4** in a 1:1 ratio. For the *trans*-fused product the enol could not be detected by spectroscopic methods. The stereochemistry of *cis*- and *trans*-**4** was determined from the ^1H NMR (*cis*-**4**: J_{ab} = 5 Hz, J_{bc} = 12.5 Hz; *trans*-**4**: J_{ab} = 11.5 Hz, J_{bc} = 12.5 Hz). The reason for the loss of stereospecificity in the cyclization of *trans*-**3** is not clear. In a control experiment the starting material was recovered after 43% conversion and shown by ^1H NMR to be >95% *trans*.[15]

The *cis*- and *trans*-annulations to 1,3-cycloheptadiene were performed in an analogous manner (Scheme 4). Again, by applying the dual stereoselectivity offered by the chloroacetoxylation approach, *cis*- and *trans*-**6**

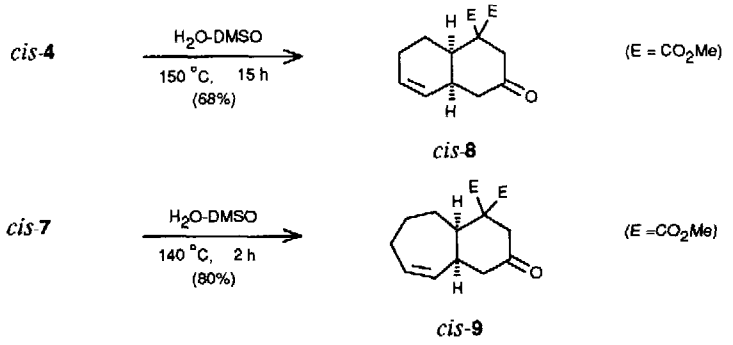
Scheme 4 (E = CO_2Me)



a. 1,4-cis-chloroacetoxylation, (ref 2a, 74%) b. $NaCHE_2$, $Pd(OAc)_2$, PPh_3 (ref 11c, 95%). c. $NaCHE_2$, CH_3CN, reflux, 18 h (88%) d. (i)NaH, **5**, NaI, THF-DMF, 25 °C (ii) MeOH, toluene, 110 °C, 24 h, (overall yield for d 46%(cis), 38% (trans)). e. $Pd(dba)_2$ or $Pd(OAc)_2$, PPh_3, NaH, THF, 65 °C, 18 - 20 h (70 - 75%)

were prepared in high stereochemical purity (> 98%). Palladium-catalyzed cyclization of compounds *cis*- and *trans*-**6** proceeded with high stereospecificity in each case. Thus, *cis*-**6** gave *cis*-**7** in 75% yield and *trans*-**6** produced *trans*-**7** in 70% yield. The stereochemistry of the products was determined from their ^1H NMR spectra (*cis*-**7**: J_{ab} = 3.5 Hz, J_{bc} = 13.1 Hz; *trans*-**7**: J_{ab} = 9.4 Hz, J_{bc} = 12.2 Hz). It is interesting to note that the carbomethoxy group α to the keto group is in an equatorial position in all of the cyclized compounds. This is most likely a result of the keto-enol equilibria leading to the thermodynamically more stable configuration.

Studies on decarboxylation of the cyclized products showed that it is possible to obtain a selective decarbomethoxylation. Thus, reaction of *cis*-**4** and *cis*-**7** with water in hot dimethylsulfoxide (DMSO)[16] afforded *cis*-**8** and *cis*-**9** respectively where only the carbomethoxy group α to the keto group was lost.



Similar *cis*- and *trans*-annulation reactions involving palladium-catalyzed reactions have recently been reported.[11a,b,17] In a closely related study the chloroacetoxylation methodology was applied to obtain stereocontrolled annulations via an intramolecular metalloene reaction.[17] The cyclization in the latter study occurred with inversion of configuration whereas the cyclization presented here occurs with retention.

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References and notes

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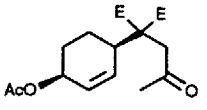
8. Attempts to cyclize the kinetic enolate of **10** or **11** (E = CO_2Me) via palladium-catalyzed reactions under a few conditions tried, has so far been unsuccessful. Cyclization of **10** at a higher temperature led to **12**. Compounds **10** and **11** are readily available from the chloroacetate **1** (ref. 7).



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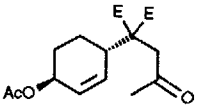

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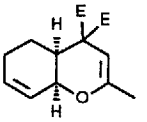

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14. The enol showed a characteristic OH signal at 12.2 - 12.4 ppm in the ^1H NMR ($CDCl_3$).
15. This would seem to indicate that isomerization of starting material *trans*-**3** to *cis*-**3** (via cis-migration of acetate from palladium to carbon in the (π-allyl)palladium intermediate) does not take place. However, if the rate of cyclization of *cis*-**3** is much faster than cyclization of *trans*-**3** the observation concerning the stereochemistry of the starting material is still compatible with an isomerization of *trans*-**3** to *cis*-**3** (cf. Nordberg, R.E.; Bäckvall, J.E. *J. Organometal. Chem.* **1985**, *C24*, 285). Other possibilities for the loss of stereospecificity could be Pd(0)(phosphine) displacement of palladium in the (π-allyl)palladium intermediate: Mackenzie, P.B.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2046.
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