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Allenylradicals in Carbocyclizations

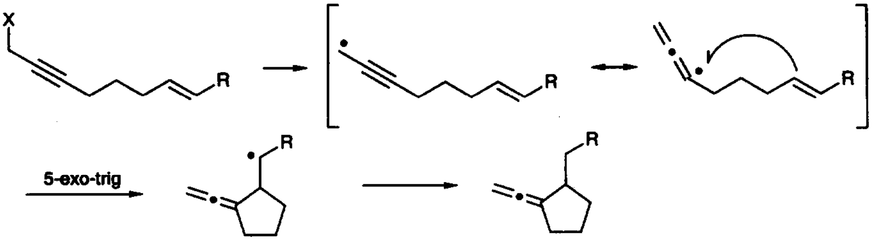
*Frank-Hardi Wartenberg, Heiko Junga and Siegfried Blechert**

Institut für Organische Chemie Technische Universität Berlin Straße des 17. Juni 135 D-1000 Berlin 12

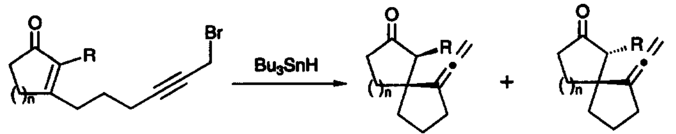
Abstract: Allenylic radicals, prepared from propargylic precursors, have been shown to cyclize diastereoselectively to vinylidene-substituted cyclopentanes.

Over the previous decades, radical-based reactions have received increasing interest in synthetic chemistry,[1] mainly due to their tolerance towards various functional groups. Especially for the construction of five-membered rings, different approaches are now well-established.[2] While propargylic moieties have been widely used as traps in radical cyclizations,[3] the use of propargylic derivatives as a radical initiator, has not yet been studied.

In this paper we wish to report on the highly diastereoselective, allenylic radical cyclization (ARC). Our strategy is based on the creation of a radical in a propargylic position. The resulting radical is stabilized by the propargylic-allenylic resonance. This ambident species has so far only been studied from a thermodynamic point of view,[4] there were no attempts to use it in a cyclization reaction. From the two canonical forms, the allenylic radical should be strongly favoured for cyclizations. To perform a ring-closure with the allenylic radical, it would be necessary to locate a multiple bond at a suitable distance.



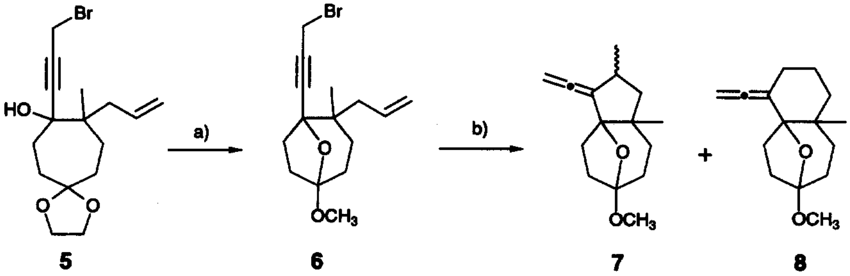
To prove this hypothesis, compound **1** was prepared[5] in four steps from 2-methyl-cyclopentane-1,3-dione. Treatment of **1** with Bu_3SnH and AIBN in refluxing benzene produced **2** in 44% yield as a mixture of diastereomers (**2a** : **2b** = 3:1). Correspondingly, **3** resulted in a 23% yield of **4**.



1 n=1 R=CH$_3$ 44% yield **2a** (3 : 1) **2b**

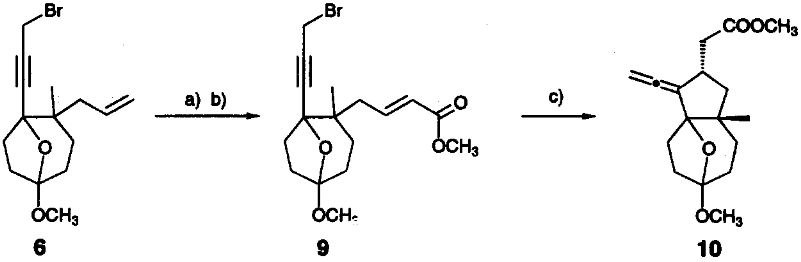
3 n=2 R=H 23% yield **4**

With these promising results in hand, we wanted to apply this method to the synthesis of hydroazulenes. A palladium-catalyzed, modified deMayo reaction recently developed in our laboratory,[6] makes 5-allylated cycloheptane-1,4-diones easily accessible. Protection of the more reactive carbonyl group and introduction of deprotonated propargyl-bromide yielded 70% of compound **5** as a 7:3 mixture of diastereomers. The diastereomers were not separated, since our main interest was the application of the novel radical cyclization. To reduce the conformational flexibility of the seven-membered ring, **5** was transformed to the isomeric **6**. This conformationally rigid, bicyclic precursor was planned to increase the discrimination of both diastereomers during the ARC. Application of the usual conditions for radical cyclizations (Bu_3SnH, AIBN, benzene, reflux) produced a complex mixture of products. The two main products were identified as **7** and **8**, with a product ratio of 3:2, in a total yield of 38%.



a) $BF_3{\cdot}OEt_2$, CH_2Cl_2, then CH_3OH, 78% b) Bu_3SnH, AIBN, benzene, 38%

To test whether this low regio- and stereoselectivity was due to electronic effects, **6** was transformed by a two-step sequence to the unsaturated ester **9**. This compound, received as a 4:3 mixture of diastereomers, was subjected to the same conditions as above and purified by preparative HPLC (RP18, $CH_3OH : H_2O = 75:25$), giving **10** in 93% yield. The product consists of two readily separable diastereomers. Their relative stereochemistry was unambiguously confirmed by NOE spectra: the methyl group and the ester moiety adopting a *trans*-relationship for both diastereomers. Thus, for **9**, the allenylic radical cyclization (ARC) to **10** proceeded with high diastereoselectivity (better than 10:1 after nmr-analysis).



a) OsO_4, $NaIO_4$, THF/H_2O b) $(EtO)_2POCH_2COOCH_3$, $NaN(TMS)_2$, THF, 45% yield overall c) Bu_3SnH, AIBN, benzene, 93%

Finally, we wanted to compare the stereochemical outcome of the ARC with established methods. Attempts to prepare **10** by the propargylic silane based Sakurai reaction[7] failed for all Lewis acids tested. Initiation by fluoride ions resulted in only 45% yield of **10**, together with the product of simple protodesilylation in 50% yield.

We have shown, that allenylic radicals perform highly diastereoselective cyclizations with enone systems. This method is an interesting alternative for the propargylic silane based Sakurai reaction. Further work is in progress to investigate the scope and limitations of this reaction.

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References and Notes

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