128. Intramolecular Vinyl Radical Cyclization Reactions of Cyclohexadienes Derived from Sequential Additions to (Arene)(tricarbonyl)chromium Complexes

Preliminary Communication

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Dedicated to the memory of our late colleague *Wolfgang Oppolzer*

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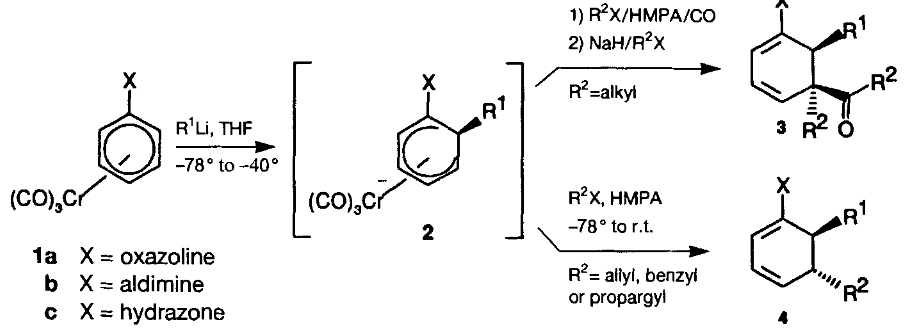
Cyclohexa-1,3-dienes **7**–**10** with a 1,5,6-substitution pattern were prepared in a one-pot reaction sequence by sequential addition of MeLi and propargyl bromides to the tricarbonylchromium complex **1a**. These products were subjected to radical cyclization procedures. Vinyl radical generation by $Bu_3Sn^{\cdot}$ addition to the propargyl group in **7**–**10** was followed by regio- and diastereoselective intramolecular ring closure. Two different *5-exo-trig* cyclizations are possible *via* different vinyl radical intermediates and cyclization to one or the other of the termini of the cyclohexadiene moiety. Internal alkynes reacted to yield exclusively the *cis*-fused hexahydroindene products **12**–**14**, whereas the terminal alkyne yielded bicyclo[3.2.1]octenes **11** as sole products.

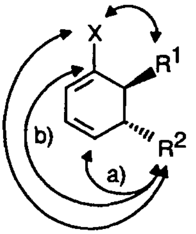
We have previously reported on the regio- and stereoselective transformation of arenes into *trans*-disubstituted cyclohexadienes by the route shown in *Scheme 1* [1]. The electrophilic $Cr(CO)_3$ group activates the arene in complexes **1** to nucleophilic *ortho*-addition of organolithium reagents. The resulting anionic cyclohexadienyl complexes **2** react with alkyl halides to give, after migratory CO insertion, reductive elimination, metal removal, and alkylation, selectively the cyclohexadienes **3**. In keeping with the lower aptitude of allyl and propargyl groups to undergo migratory CO insertion, allyl and propargyl halides give cyclohexadienes **4** with good selectivity. Successful asymmetric methodologies, developed for these one-pot reaction sequences include the use of either a chiral auxiliary X (*e.g.* a chiral oxazoline [2]) and of ligands which chirally modify the R^1Li reagents [3].

Scheme 1



1a X = oxazoline
b X = aldimine
c X = hydrazone

Both dihydroarenes **3** and **4** offer a number of possibilities for polar, radical (for a review, see [4]) or transition-metal-mediated [5] [6] intramolecular diastereoselective cyclization reactions. For **4**, these are schematically shown below. In this communication, we report on the transformation of the alkynyl moiety (**4**, R^2 = propargyl) to a vinylic radical and on the regioselectivity of the ensuing cyclization to the diene system (connectivity *a* or *b*).



The starting materials, propargyl-cyclohexadienes **7**–**10**, were prepared by the sequential addition of nucleophile/electrophile, *i.e.*, MeLi and propargyl bromides, to the (tricarbonyl)(phenyloxazoline)chromium complex **1a**. Radical cyclization reactions were then carried out by addition of Bu_3SnH (1.6 equiv.) to a solution of **7**–**10** (0.7M)¹) and azabis[isobutyronitrile] (AIBN) in benzene at 80° (*Scheme 2*).

Under the above conditions, **7** (R = H) was selectively transformed into the bicyclo-[3.2.1]octenes **11a**²) and **11b**²) (65:35 ratio) in 67% yield. This suggests addition of the $Bu_3Sn^\cdot$ radical to the α-position of the alkyne to give intermediate **A** (for precedents, see [7]), followed by a *5-exo-trig* cyclization [8] to C(1) of the cyclohexadiene and Bu_3SnH reduction of the resulting allylic radical intermediate. A different pathway is followed in analogous reactions with **8**–**10**, where R ≠ H. The single products obtained are the *cis*-tetrahydroindenes **12**–**14**²). We conclude that they are formed *via* intermediate **B** which then undergoes cyclization, followed by reduction (*Scheme 2*). Thus, compounds **7**–**10** have the attractive feature that both accessible regioisomeric vinyl radicals have the possibility to undergo a *5-exo-trig* cyclizations. The observation is that the terminal alkyne follows highly selectively one pathway and internal alkynes the other.

Two hypotheses may be considered in explaining the observed regioselectivity. In the first one, we assume (as postulated by *Stork* and *Mook* [9]) that the two radical intermediates **A** and **B** are formed in each case, and that they are in equilibrium because of the reversibility of the $Bu_3Sn^\cdot$ addition. Cyclization to C(1) may be electronically favored by the proximity of the oxazoline group, and this pathway is followed when R = H. When R ≠ H, steric congestion between the substituent R and the oxazoline group may adversely affect addition to C(1). Equilibration of the radicals **A** and **B** then redirects addition *via* the second *5-exo* cyclization to C(4). The second hypothesis is that **A** and **B** are not in equilibrium. The products then reflect the high regioselectivity of the $Bu_3Sn^\cdot$ addition to the alkyne.

First experiments to clarify this mechanistic question were carried out. The structure of the starting material was modified in such a way as to render a *5-exo-trig* cyclization pathway *via* **A** impossible. This was achieved *via* selective hydrogenation of the

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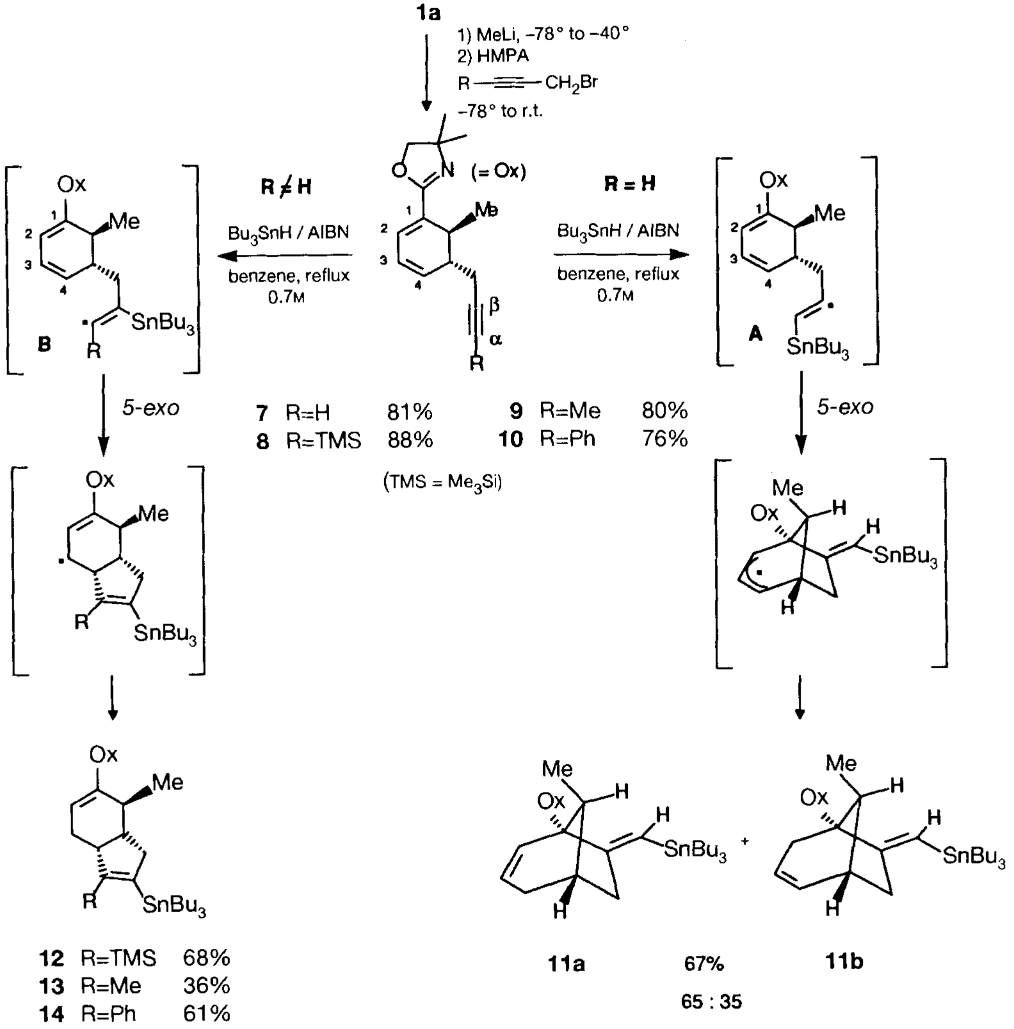
¹) No radical cyclization occurred at low concentration (0.02M).

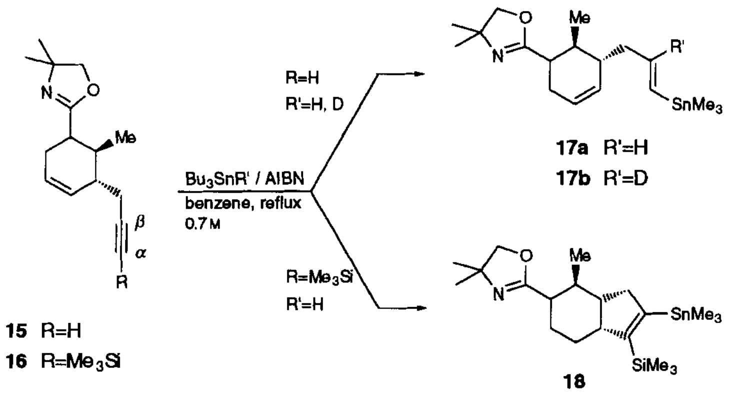
²) Structures shown are based on spectroscopic analysis (^1H- and ^{13}C-NMR, and NOESY correlation).

Scheme 2



C(1)=C(2) bond in **7** and **8** with DIBAL to yield **15** (57%) and **16** (40%). The selective reduction of the alkene moiety adjacent to the oxazoline moiety is likely the result of coordination of the Al reagent to the oxazoline before the hydride transfer. If the vinyl radical intermediates **A** and **B** are in equilibrium, the reaction sequence should yield the *cis*-fused hexahydroindene in both cases. While **16** underwent reaction to give **18** (32%), the propargyl diene **15** exclusively yielded the reduction product **17a** (46%) (*Scheme 3*). As **15** may be predisposed to undergo intramolecular H transfer from C(1) to the vinyl radical, the reaction was repeated with Bu_3SnD. The deuterium was incorporated solely in the vinylic position (**17b**, 68%), thus ruling out intramolecular H transfer. These preliminary results show that only one vinylic radical is formed from **15**, and that its reaction with Bu_3SnH is faster (to yield **17**) than its equilibration to its regioisomer.

Scheme 3



In conclusion, we have found a convenient access to the diastereoisomerically pure tetrahydroindene **12**–**14** and bicyclo[3.2.1]octene **11**. The formation of the bicyclic products is dependent upon the substitution of the acetylenic moiety. We note that bicyclo[3.2.1]octenes containing an *exo*-methylidene group are part of the skeleton of a number of natural products (*e.g.* kaurane) [10].

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