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PREPARATION OF CYCLOHEXENYL DERIVATIVES BY THE RING-OPENING REACTIONS OF OXABICYCLO[2.2.1] COMPOUNDS WITH CUPRATES

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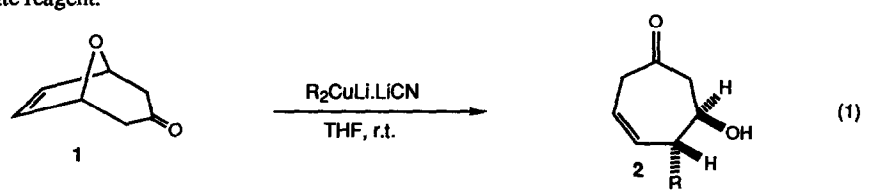
Abstract: The ring-opening reaction of 7-oxabicyclo[2.2.1]hept-5-enes with cuprates is described. S_N2' attack with retention of configuration is the predominant pathway.

We recently reported that reaction between 8-oxabicyclo[3.2.1]oct-6-en-3-one and an organocuprate yields cycloheptenones **2** with good levels of regio- and stereocontrol, eq.1.[2] One feature of this reaction is that the products derived from this opening are regioisomeric with those from the analogous opening of a vinylepoxide with a cuprate reagent.[3-5]

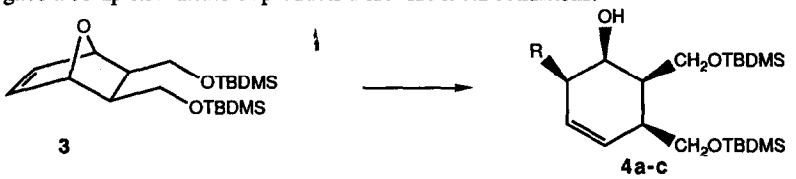


(1)

In general, good yields of the hydroxycycloheptenones were obtained with a variety of different cuprate sources and alkyl lithium precursors. In that work, we noted that conversion of the carbonyl group to an olefin caused the reactivity of the substrate to decrease dramatically such that no opening occurred. As this result was unexpected, we decided to expand our studies to include an exploration of the reactivity of 7-oxabicyclo[2.2.1] compounds. We anticipated that, while they lacked a carbonyl group, their ring openings were likely to be more facile as a result of higher strain. Concurrent with our research was that of Fernandez de la Pradilla and coworkers who made the serendipitous observation that 7-oxabicyclo[2.2.1]hept-5-en-2-ones react in the presence of organolithium reagents to give cyclohexenediols via a double addition of the organolithium.[6] In this report, we describe the reactivity of 5- and 5,6- disubstituted oxabicyclic compounds **3**, **5** and **8a,b** with organocuprates to make highly substituted cyclohexenol derivatives.

Rickborn reported that an unsubstituted 7-oxabicyclic [2.2.1] compound failed to react with lithium dimethylcuprate at -78 °C.[7] These results did not discourage this line of study since we had previously observed that the reaction temperature was a crucial factor in order to achieve ring-opening. Nevertheless, we initially chose symmetrical substrates for exploration to minimize the number of regioisomers and focus instead on the stereochemistry of the opening. Compound **3** was readily prepared via cycloaddition between furan and maleic anhydride followed by reduction (LAH, ether) and protection (TBDMSCl, imidazole, DMF).[8] Treatment with an organocuprate derived from copper cyanide (1 eq.) and the appropriate organolithium (1.8 eq.) in THF at room

temperature gave cyclohexenols as shown in the Table. $Me_2CuLi{\cdot}LiCN$ and $n\text{-}Bu_2CuLi{\cdot}LiCN$ (5.0 eq. in THF at r.t) failed to react under the conditions which were successful for the [3.2.1] substrates. The use of $BF_3{\cdot}Et_2O$ to catalyze the ring-opening was also explored without success.[9] However, when the more reactive secondary or tertiary organolithium was used as a precursor to the cuprate, opening occurred very smoothly to give **4b,c** in excellent yields, entries 4,5.[10] Following the report of Fernandez de la Pradilla, we examined the reaction of **3** with n-BuLi and t-BuLi in ether at 0 °C. Ring opening occurred cleanly with n-BuLi providing adduct **4a** in good yield but t-BuLi gave a complex mixture of products under identical conditions.



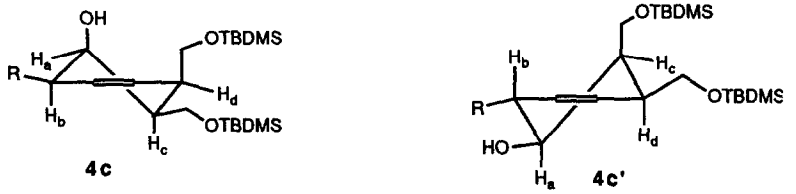
3 **4a-c**

Table 1. Reaction of 7-Oxabicyclo[2.2.1]hept-5-ene **3** with Organocuprates

Entry	RLi	Copper Source	Conditions	Product(s)	Yield[1]
1	MeLi	CuCN	THF, 0 °C to r.t.	N.R.	--
2	n-BuLi	CuCN	THF, 0 °C to r.t.	N.R.	--
3	n-BuLi	--	ether, 0 °C	**4a** R=n-Bu	73%
4	s-BuLi	CuCN	THF, 0 °C to r.t.	**4b** R=s-Bu	78%
5	t-BuLi	CuCN	THF, 0 °C to r.t.	**4c** R=t-Bu	85%
6	t-BuLi	--	ether, 0 °C	complex mixture	

1. Yield of isolated product following purification by flash chromatography.

In adducts **4a-c**, attack occurred at one site in the bicyclic ring yielding a single regio- and stereoisomer as determined from their ^1H and ^{13}C NMR spectra. Two regioisomers and two stereoisomers are possible from the opening. Decoupling experiments on **4c** established that the secondary carbinol hydrogen H_a was not coupled to either of the olefinic protons but it was coupled to H_b and H_c. Thus ring opening had occurred in an S_N2' fashion as opposed to a direct S_N2 displacement. Furthermore, consideration of the two possible stereoisomeric products derived from S_N2' attack indicated that the overall stereochemistry of addition was *syn*! The proton H_a in **4c** appears as a broad multiplet. H_a is coupled to the H_b and H_c with coupling constants of < 3 Hz while the expected J-values for H_a-H_b in the stereoisomeric product **4c'** would be 10-12 Hz.[11] Thus, the compounds **4** are regio- and stereoisomeric to those available from the cuprate opening of a cyclohexenylepoxide.[4] Most interestingly, stereoisomeric products to the analogous [3.2.1] opening were obtained.

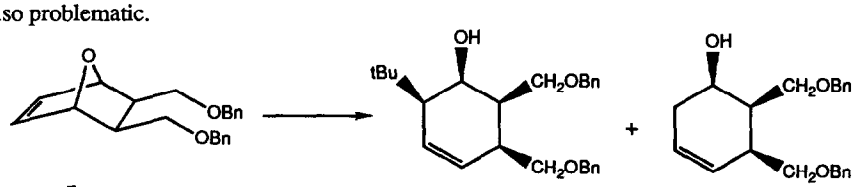


4c **4c'**

One of several mechanistic possibilities could rationalize our results. While the usual stereochemical pathway followed in cuprate reactions is with inversion of stereochemistry at the centre undergoing attack,[5]

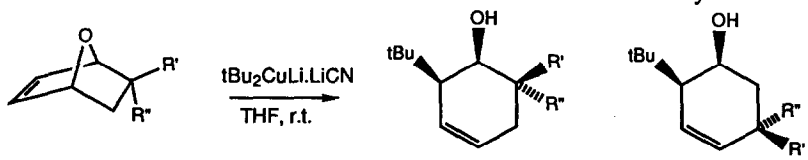
displacements with retention of stereochemistry are known to occur and be dependant on the nature of the leaving group. Specifically, Goering has shown that leaving groups which are also capable of coordination direct the incoming nucleophile to one face of the olefin.[12a] In our system, coordination of the lithium cation to the oxygen of the oxabicyclic ring could trigger the opening which is then rapidly trapped by the cuprate. Alternately, coordination of the cuprate to the least hindered face of the bicyclic framework and insertion into the C-O bond with retention of configuration could take place.[12b] Reductive elimination of a copper (III) species would yield the product. Carbocupration of the strained olefin from the exo face followed by an elimination is another option which cannot be ruled out at this time.[12c] From the change in stereochemistry observed for the [3.2.1] vs. [2.2.1] systems and the observation that the [2.2.1] system does not require the presence of the carbonyl group, it seems clear that the higher strain in the latter cases makes ring-opening a more facile process.

Having demonstrated the viability of effecting the desired ring-opening, we examined the compatibility of other commonly used protecting groups. When **5** was reacted with t-Bu_2Cu·LiCN under identical conditions we observed ring opened adduct **6** along with a reduced product **7** in a 3:1 ratio. In this reaction, a diminished yield (48%) along with substantial recovered starting material (45%) was observed. We suspect that competitive coordination to the ether oxygens may be occurring in this substrate since use of a paramethoxybenzyl protecting group was also problematic.



5 **6** **7**

With the stereochemistry determined we next set out to examine the regioselectivity. The unsymmetrical oxabicyclic compounds **8a,b** were prepared using standard methods.[13] When **8a** was treated under the usual conditions we isolated two products in 95% yield as a 60:40 mixture of isomers as measured by G.L.C. Extensive decoupling experiments on the pure isomers showed that while high stereocontrol had occurred in the opening (the t-Bu and OH were cis), the two possible regioisomers from S_N2' attack were obtained. Similar results were obtained with the endo isomer **8b** in which **9b** and **10b** were isolated in 88% combined yield.



8a R'=CH_2OTBDMS, R"=H
b R'=H, R"=CH_2OTBDMS

9a **b**

10a **b**

In conclusion we have shown that oxabicyclo[2.2.1] systems are reactive toward cuprate reagents[14] under the conditions previously described for the [3.2.1] compounds. There is clearly a very delicate balance between reactivity of the substrates and the nucleophiles in this reaction. The stereochemical differences indicate that a different mechanism may be operating in the two classes of substrates. At the present time, the method is limited to secondary and tertiary organolithium precursors. Nevertheless, organocuprates exhibit substantially higher chemoselectivity toward several functional groups compared to the corresponding organolithium reagents which

suggests this method may have value in the ring-opening of polyfunctional substrates. Four contiguous stereocentres are created in the cycloaddition-opening sequence.

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References and Notes

1. NSERC(Canada) University Research Fellow 1987-1992. Bio-Mega Young Investigator Awardee, 1990-92.

2. Lautens, M.; Di Felice, C.; Huboux, A. *Tetrahedron Lett.* **1989**, 30, 6817. We assigned the stereochemistry of the opening on the basis of ^{1}H NMR coupling constants. Due to the uncertainty of such assignments in seven-membered rings, we have carried out an X-ray crystallographic analysis of the product derived from reaction with $tBu_2CuLi{\cdot}LiCN$ and confirmed our original assignment.

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7. Staroscik, J.; Rickborn, B. *J. Am. Chem. Soc.* **1971**, 93, 3046.

8. The cycloaddition was first reported by Diels and Alder, see: Diels, O.; Alder, K. *Chem. Ber.* **1929**, 62, 554.

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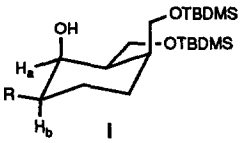
10. Satisfactory NMR, IR, and mass spectra and/or combustion analyses were obtained for all new compounds.

11. Hydrogenation of the olefin (H_2, 10% Pd-C, EtOAc, 48 h.) gave the substituted cyclohexane **i**. H_a appeared as a broad singlet with a width at half height of <4 Hz. Energy minimization (MM2) indicated that the coupling constant $J_{a\text{-}b}$ would be 0.2 Hz for the isomer shown while the expected value for the stereoisomer would be 11.2 Hz further supporting our stereochemical assignment.



I

12. a) Goering, H.L.; Kantner, S.S.; Tseng, C.C. *J. Org. Chem.*, **1983**, 48, 715 and references therein. b) For a recent discussion of the mechanisms of S_N2' displacements in cuprate reactions, see: Corey, E.J.; Boaz, N.W. *Tetrahedron Letters*, **1985**, 26, 6015 and references therein. c) Caple, R.; Chen, G. M.-S., Nelson, J.D. *J. Org. Chem.* **1971**, 36, 2874.

13. Compounds **8a,b** were prepared by BF_3 catalyzed cycloaddition of furan and methyl acrylate, separation of the exo and endo isomers, reduction ($LiAlH_4$, ether) and protection (TBDMS-Cl, imidazole, DMF). For the cycloaddition reaction, see: Kotsuki, H.; Asao, K.; Ohnishi, H. *Bull. Chem. Soc. Jpn.* **1984**, 57, 3339.

14. In a typical procedure: CuCN (2.5 mmol) was dried with a hot-gun under vacuum for 5 min. before suspending the solid in THF. The vessel was cooled to -78 °C and the organolithium (4.9mmol) was introduced dropwise over 2-5 min. Upon completion of the addition, the cuprate solution was warmed to 0 °C and stirred for 1 h. The oxabicyclic substrate (1 mmol) was dissolved in THF and added dropwise to the cuprate via cannula over 5-10 min followed by warming the reaction to room temperature where it was stirred until t.l.c. indicated the starting material was consumed. Ammonium chloride was added and the mixture exposed to the air. Filtration of solids through Celite-silica gel gave a clear solution which was worked-up and purified using standard techniques.

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