Tetrahedron Letters, Vol.32, No.37, pp 4827-4830, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

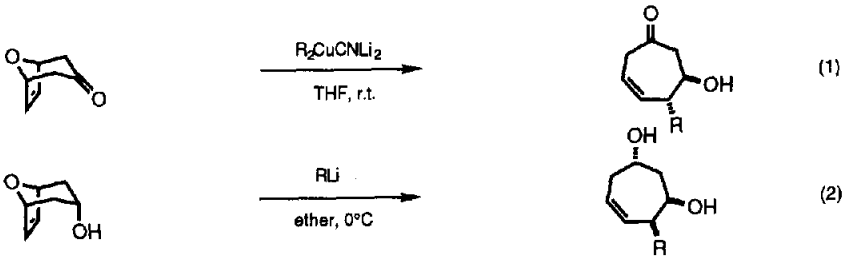
THE REDUCTIVE RING-OPENING OF OXABICYCLIC COMPOUNDS

Mark Lautens*,[1a] Pauline Chiu[1b]

Department of Chemistry, University of Toronto
Toronto, Ontario, Canada M5S 1A1

Abstract: Oxabicyclo[3.2.1]octenes and [2.2.1]heptenes have been found to undergo reductive ring-opening when treated with organolithium or organomagnesium reagents with added magnesium bromide.

We have recently reported the ring-opening reactions of oxabicyclo[3.2.1] compounds with organocuprates and organolithium reagents, yielding 1,2-disubstituted cycloheptenes with complimentary relative stereochemistry, eq. 1, 2.[2] In contrast to the results with [3.2.1] systems, oxabicyclo[2.2.1] compounds undergo ring-opening with cuprates and organolithium reagents with identical stereochemistry.[2,3] Of the nucleophiles reported thus far, the simplest nucleophile, i.e. hydride, was incapable of cleaving the bridging C-O bond.[4] In this paper, we report that organomagnesium or organolithium reagents bearing β-hydrogens cause a reductive ring-opening of oxabicyclo[3.2.1] and [2.2.1] systems *in the presence of excess magnesium bromide.*

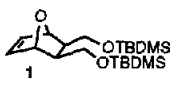
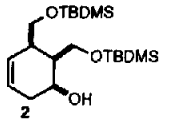
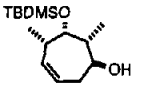
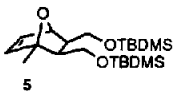
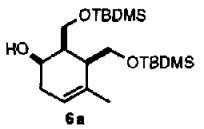
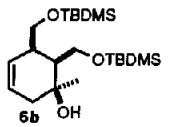
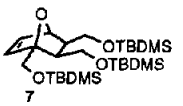
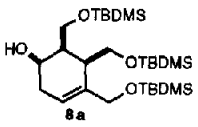
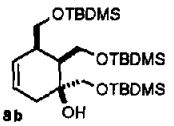
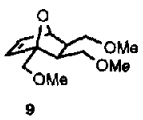
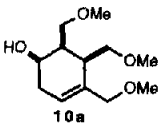
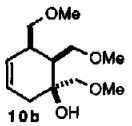


(1)

(2)

In the course of examining nucleophiles other than cuprates and lithium reagents, we treated substrates **1** and **2** with other organometallic compounds. For example, treatment of **1** with *t*-BuLi in the presence of zinc chloride yielded the expected ring-opened product from the addition of a *t*-butyl group. The use of an organomagnesium reagent proved to be more interesting. The oxabicyclo[3.2.1]octene **3b** reacted slowly with 1:1 *n*-BuLi:$MgBr_2$ at room temperature over several days to give a mixture of products. In an effort to increase the rate of the reaction, excess magnesium bromide was added, the rationale being that the complexation of the Lewis acid

Table Reductive Ring-Opening of Oxabicyclic Compounds

Entry	Oxabicyclic Compound	Hydride Source[1]	Product	Yield[2]
1	 1	A	 2	68%
		B		76%
2				
	3 a) R=H	A or B	4	N.R.
	b) R=TBDMS	A		66%
		B		see footnote[3]
3	 5	A	1.2 : 1  6a  6b	50%
		B	1 : 2.4	37%
		C	1 : 4.5	44%
4	 7	A	3.6 : 1  8a  8b	83%
		B	2 : 1	88%
		C	1 : 3.5	42%
5	 9	A	1 : 2.4  10a  10b	55%
		B	1 : 1	24%
		C	2.5 : 1	21%

1. A= 5 eq. t-BuLi, 10 eq. $MgBr_2$, B= 5 eq. n-BuLi, 10 eq. $MgBr_2$, C= 5 eq. i-BuMgCl, 10 eq. $MgBr_2$. 2. Isolated yields of the mixture of isomers, analytically pure material. 3. Reaction was slower, product not isolated.

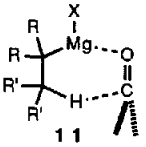
to the bridging oxygen could enhance nucleophilic attack.[5] Under these conditions, the major compound obtained was **4**, the product of hydride delivery.[6] Similarly, treatment of **1** with *n*-BuLi and excess magnesium bromide produced **2**. We had previously observed trace amounts of this compound in reactions of **1** with organocuprate

reagents.[3a] An examination of different solvents showed that in THF, precipitation of a white solid occurs and no reduction is observed. Toluene and ether are both effective solvents with the latter showing the faster rates of reaction. With these results in hand, we have examined the reduction of other oxabicyclic compounds and have shown the reductive ring-opening to be general and, in some instances, modestly regioselective (see Table). Notably, all these reactions are sluggish, typically requiring 48-96 h. Five equivalents of *n*-BuLi or *t*-BuLi along with ten equivalents of freshly prepared magnesium bromide were suitable sources of hydride as was isobutylmagnesium chloride plus 10 equivalents $MgBr_2$. In general, *t*-BuLi/$MgBr_2$ reduced all of the oxabicyclo[2.2.1] substrates faster than either *n*-BuLi/$MgBr_2$ or *i*-BuMgCl/$MgBr_2$, presumably due to the increased number of β-hydrogens available for reduction.[7]

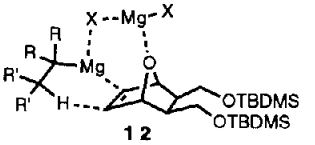
Little is known about the regioselectivity of the opening of unsymmetrical oxabicyclic substrates with organocuprates or lithium reagents.[8] Substrates **5**, **7**, and **9**, each bearing a substituent at the bridgehead position, were readily prepared from 2-substituted furans via Diels-Alder cycloadditions with maleic anhydride, followed by reduction with lithium aluminum hydride and protection of the resulting alcohols.[9] Regioselective ring-opening of the unsymmetrical [2.2.1] substrates was observed and the level of selectivity found to vary as a function of the source of hydride and the substituent at the bridgehead position. For example, **5** undergoes non-selective opening via attack of hydride when *t*-BuLi is used, but the selectivity improved to 4.5:1 in favor of attack at the more hindered position when *i*-BuMgCl was used. *n*-BuLi was of intermediate selectivity. This selectivity parallels the increase in β-substitution for the various hydride sources and presumably the relative steric hindrance between the β carbons with the substrate. Substrate **7**, which has a more sterically demanding substituent, shows a tendency to undergo attack at the position distal to the substituent, the preference also diminishing with increasing substitution at the β-position of the hydride delivery agent.[10] While it is difficult to explain the magnitude of the selectivity toward the various reagents (entries 3 and 4), the trend is consistent, that is, as the steric hindrance at the β position of the hydride source increases (and the hindrance at the α carbon decreases) under conditions A, B, and C, the tendency to attack at the more hindered carbon increases.

The reductive opening of **9** shows the opposite trend. In this instance, the selectivity toward attack at the carbon distal to the substituent increases with increasing substitution at the β-carbon of the hydride source. We attribute this change to the simultaneous chelation of magnesium to the bridging oxygen and the methoxymethyl group, directing the hydride to the distal carbon.

The role of magnesium bromide appears to be two-fold. Conversion of the organolithium compound to an organomagnesium compound occurs first. However, this cannot be the only role of magnesium since the addition of only one equivalent fails to promote the ring opening. It seems unlikely that *in situ* generation of a metal hydride occurs as this is inconsistent with the changing regioselectivity as a function of the Grignard reagent. Furthermore, magnesium bromide cannot be simply catalyzing the ring-opening of the substrate to form a cationic intermediate which is subsequently reduced, since **6a** should then be formed in preference to **6b**. Complexation



11



12

of the magnesium to the bridging oxygen seems likely and the attack of the hydride is expected to occur from the endo face in keeping with the stereochemistry of organolithium additions. In analogy to the reduction of carbonyl groups by the delivery of a β-hydride, i.e. **11**, structure **12** represents an illustration of our working model depicting the transition state leading to reductive ring-opening.

In summary, we have shown that reductive ring-opening of oxabicyclic compounds is possible using Grignard reagents bearing β-hydrogens and that moderately regioselective opening is possible. The sense of the regioselectivity is influenced by the substrate *and the hydride source*. These phenomena are currently under investigation so as to more clearly define the contributing factors with the ultimate goal of improving the selectivity.

Acknowledgments. This research was supported by the Alfred P. Sloan Foundation, the Natural Sciences and Engineering Research Council (NSERC) of Canada, Bio-Mega Inc., the Bickell Foundation and the University of Toronto.

References and Notes

1. a) Alfred P. Sloan Foundation Fellow 1991-1993; NSERC(Canada) University Research Fellow 1987-1992, Bio-Mega Young Investigator 1990-1993. b) NSERC(Canada) Postgraduate Scholar 1989-92.
2. a) Lautens, M; DiFelice, C.; Huboux, A. *Tetrahedron Lett.*, **1989**, 30, 6817. b) Lautens, M.; Abd-El-Aziz, A.S.; Lough, A. *J. Org. Chem.* **1990**, 55, 5305.
3. a) Lautens, M.; Smith, A.C.; Abd-El-Aziz, A.S.; Huboux, A.H. *Tetrahedron Lett.* **1990**, 31, 3253. b) Arjona, O.; Fernandez de la Pradilla, R.; Garcia, E.; Martin-Domenech, A.; Plumet, J. *Tetrahedron Lett.* **1989**, 30, 6437.
4. Reagents such as $LiAlH_4$ do not cause cleavage of the bridging C-O bond.
5. Boron trifluoride has previously been used to promote the ring-opening of an oxabicyclic compound using thiophenol as the nucleophile, however, the reaction was non-regioselective, see: Rigby, J.H.; Wilson, J.A.Z. *J. Org. Chem.* **1987**, 52, 34.
6. Satisfactory ^1H and ^{13}C NMR, IR, and mass spectral data and/or C,H analyses were obtained for all new compounds.
7. A typical experimental procedure is as follows: To 0.6 mL of a 1.3 M $MgBr_2$ etherate solution (0.8 mmol) was added 1 mL dry ether, followed by 0.23 mL of 1.7 M ^tBuLi (0.4 mmol). After stirring for 5 minutes at room temperature, **1** (337 mg, 0.08 mmol) was added as a solution in 1 mL dry ether. After 72 hours at room temperature, the reaction mixture was cooled to 0°C, diluted with ether and quenched with saturated NH_4Cl solution. Compound **2** (257 mg, 76% yield) was obtained following flash chromatography.
   Characterization of **2**: ^1H NMR: δ 5.68 (dm, 1 H, J=10.1 Hz), 5.44 (dm, 1 H, J=10.1 Hz), 4.54 (d, 1 H, J=10.0 Hz), 3.89 (ddt, 1 H, J=10.2, 5.4, 2.7 Hz), 3.82 (d, 2 H, J=7.9 Hz), 3.67 (dd, J= 10.3, 4.2 Hz), 3.49 (dd, 1 H, J=10.3, 5.4 Hz), 2.54 (m, 1 H), 2.33 (dt, 1 H, J= 8.1, 2.7 Hz), 2.32 (m, 1H), 2.18 (dddd, 1 H, J= 17.7, 7.5, 4.2, 2.1 Hz), 0.88 (s, 9 H), 0.87 (s, 9 H), 0.053 (s, 9 H), 0.047 (s, 3 H); ^{13}C NMR: δ 127.2, 126.2, 67.0, 62.5, 62.5, 41.6, 39.3, 33.7, 25.7, 25.6, 18.1, 17.9, -5.8.
8. For an example where an electron-withdrawing group directs the site of attack, see: Arjona, O.; Fernandez de la Pradilla, R.; Mallo, A.; Plumet, J.; Viso, A. *Tetrahedron Lett.* **1990**, 31, 1475.
9. Brown, G.M.; Dubreuil, P. *Can. J. Chem.* **1968**, 46, 1577.
10. For a discussion of reduction of carbonyl groups by Grignard reagents bearing β-hydrides, see: Singer, M.S.; Salinger, R.M.; Mosher, H.S. *J. Org. Chem.* **1967**, 32, 3821 and references therein. For a review on the Meerwein-Ponndorf -Verley reduction, see: Wilds, A.L. *Org. React.*, **1944**, 2, 178. Samarium alkoxides have also been used to effect this reduction, See: Namy, J.L.; Souppe, J.; Collin, J.; Kagan, H.B. *J. Org. Chem.* **1984**, 49, 2045.

(Received in USA 24 April 1991)