Tetrahedron Letters,Vol.28,No.45,pp 5547-5548,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

STEREOSELECTIVITY OF THE REACTION BETWEEN 7-OXABICYCLO[2.2.1]HEPT-5-EN-2-ONE AND ORGANOCUPRATE REAGENTS

Odón Arjona, Roberto Fernández de la Pradilla, Cristina Manzano, Sonia Pérez and Joaquín Plumet*

Departamento de Química Orgánica, Facultad de Química,
Universidad Complutense, E-28040 Madrid, Spain.

Summary. Lithium organocuprates add with high stereoselectivity to the hindered *endo* face of the carbonyl group of 7-oxabicyclo[2.2.1]hept-5-en-2-one to yield the corresponding *exo* alcohols.

The stereochemical outcome of nucleophilic additions of organolithium and Grignard reagents to bicyclic ketones is a well documented process[1]. Thus, the reaction of the readily available optically pure 7-oxabicyclo[2.2.1]hept-5-en-2-one[2] **1** with a variety of organolithium and Grignard reagents yielded the expected *endo* alcohols **2** with very high stereoselectivity[3]. The preparation of the *exo* isomers **3** was then addressed. For this purpose, the reagent developed by Macdonald and Still[4], prepared by addition of MeLi to Me_2CuLi, was perceived as an appealing possibility. It was envisioned that coordination of the "unreactive"[5] lithium dimethylcuprate with the carbonyl group[6a] and with the oxygen brigde[6b] should block the *exo* face of **1**, thus forcing nucleophilic attack by methyllithium to occur from the *endo* face of the molecule. The results obtained are summarized in the Table[7].

1 **2** **3**

Entry	R	R'	2/3 ratio	Yield (%)[a]
1	Me	Me	1:6	80
2	n-Bu	n-Bu	b	70
3	Ph	Ph	10:1	75
4	–	Me[c]	1:6	85
5	–	n-Bu[c]	b	75
6	–	Ph[c]	1:6	85

a) Yields of pure, isolated products. b) Only *exo* isomer (**3**) was detected. c) The reaction was conducted exclusively with R'$_2$CuLi.

When **1** was treated with MeLi-Me_2CuLi (3 equivalents), a mixture of alcohols **2** and **3** in a 1:6 ratio was obtained. The introduction of a *n*-butyl group was effected in a similar fashion; these results seemed to confirm our hypothesis. However, the reaction of **1** with

PhLi-Ph_2CuLi yielded a 10:1 mixture of 2 and 3, perhaps indicating that nucleophilic addition was taking place faster than complexation in this case[8].

In order to check that the cuprate did not react with the carbonyl group, the reaction of 1 with Me_2CuLi was examined (entry 4). Surprisingly, a mixture of 2 and 3 was obtained in identical ratio as when MeLi-Me_2CuLi had been utilized; analogous behavior was observed for *n*-Bu_2CuLi and Ph_2CuLi yielded a 1:6 mixture of 2 and 3. In all cases, the reactions were instantaneous and required an excess of cuprate.

The reaction of 1 with *simple* lithium organocuprates in an instantaneous manner and in high yields is unprecedented in the literature. The dramatic *reversal* of stereoselectivity, with respect to organolithium and Grignard reagents, is a unique phenomenon[4], formally analogous to the use of MeLi-MAD for the preparation of equatorial cyclohexanols[9]. The scope and synthetic potential of this methodology (an example of which is described in the following report) as well as the clarification of the mechanism of the process are currently being explored in our laboratories.

Acknowledgments. One of us (RFP) gratefully acknowledges the Dirección General de Política Científica (Ministerio de Educacion y Ciencia, Spain) for a postdoctoral fellowship. We acknowledge support by CAICYT (Grant No. 0320-84).

References and Notes.

1.- a) J. R. Boone, E. C. Ashby, Top. Stereochem., (1979), 11, 53; b) E. C. Ashby, J. T. Laemmle, Chem. Rev., (1975), 75, 521. 2.- a) E. Vieira, P. Vogel, Helv. Chim. Acta, (1983), 66, 1865; b) K. A. Black, P. Vogel, Ibid., (1984), 67 , 1612. 3.- C. Manzano, Ph. D. thesis research. These results will be published elsewhere. This behavior is consistent with literature data for norbornenic systems. See: a) W. L. Brown, A. G. Fallis, Tetrahedron Lett., (1985), 26, 207; b) M. E. Jung, G. L. Hatfield, Tetrahedron Lett., (1983), 24, 2931. 4.- a) T. L. Macdonald, W. C. Still, J. Am. Chem. Soc., (1975), 97, 5280; b) T. L. Macdonald, W. C. Still, Tetrahedron Lett., (1976), 2659. 5.- Lithium organocuprates are generally unreactive towards saturated ketones. For some reports of organocuprates/ketone additions see: a) L. T. Scott, W. D. Cotton, J. Chem. Soc. Chem. Commun., (1973), 320; b) D. J. Goldsmith, I. Sakano, Tetrahedron Lett., (1974), 2857; c) H. D. House, C. Y. Chu, J. M Wilkins, M. J. Umen, J. Org. Chem, (1975), 40, 1460; d) J. P. Marino, D. M. Floyd, Tetrahedron Lett., (1975), 3897. 6.- a) E. C. Ashby, S. A. Noding, J. Org. Chem., (1979), 44 4371; Lipshutz reports that the addition of 3 equivalents of RLi to CuI affords only R_2CuLi + free RLi. See: B. H. Lipshutz, Synthesis, (1987), 325; b) It has been recently reported that an ortho-methoxymethyl substituent in a methyl cinnamate system intramolecularly assists the conjugate addition of Me_2CuLi. See: G. Hallnemo, C. Ullenius, Tetrahedron Lett., (1986), 27, 395. 7.- The stereochemistry of these alcohols was assigned on the basis of their ^{1}H-NMR spectra. For example, the *exo* isomer 3 (R = Me) presents a remarkably shielded methyl group (1.20 ppm), with respect to the *endo* isomer 2 (R = Me, 1.52 ppm). These observations are consistent with the expected influence of the anisotropic double bond, a well established phenomenon; see L. M. Jackman, S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd edition, Pergamon Press, p.84. For further evidence see next paper in this issue (formation of oxetane 7 from *endo*-alcohol 3). 8.- There are numerous examples in the literature of the "anomalous" behavior of the vinyl and phenyl cuprates. See, for example J. P. Marino and J. C. Jaén, J. Am. Chem. Soc., (1982), 104, 3165. 9.- a) For the use of MeLi-MAD, see: K. Marnoka, T. Itoh, H. Yamamoto, J. Am. Chem. Soc., (1985), 107, 4573. b) For a recent example of axial selectivity in nucleophilic additions of lithioacetonitrile to cyclohexanones, see: B. M. Trost, J. Florez, D. J. Jebaratnam, J. Am. Chem. Soc., (1987), 109, 613.

(Received in UK 9 September 1987)