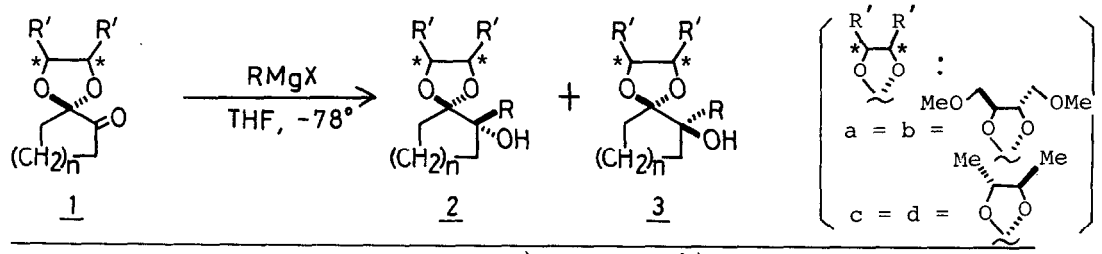
Tetrahedron Letters, Vol.27, No.1, pp 81-82, 1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

DIASTEREOSELECTIVE ADDITION OF GRIGNARD REAGENTS TO CHIRAL α-KETOACETALS

Yasumitsu Tamura,* Hiroshi Kondo, Hirokazu Annoura,
Ritsuko Takeuchi, and Hiromichi Fujioka
Faculty of Pharmaceutical Sciences, Osaka University
1-6, Yamada-oka, Suita, Osaka 565 Japan

Summary: High diastereoface-differenciating addition occurred in the reaction of chiral cyclic α-ketoacetals 1a and 1b with Grignard reagents.

The chiral acetals derived from chiral diols with C_2 axis of symmetry have been recognized as very useful chiral auxiliaries in some asymmetric reactions such as asymmetric cyclization reaction,[1a] Lewis acid catalyzed coupling of chiral acetals with organosilicon compounds,[1b] reaction of chiral acetals with organometallic compounds,[1c] asymmetric bromolactonization using chiral acetals,[1d] and remote acyclic stereocontrol reaction.[1e] Here we wish to describe that the addition of Grignard reagents to chiral α-ketoacetals(1a,1b) proceeds in high diastereoselective manner. The asymmetric nucleophilic



1 2 3

run	substrate	RMgX[a)]	yield[b)]	ratio(2:3)
1	1a (n=2)	MeMgBr	93	2a only[c)]
2	1b (n=1)	MeMgBr	91	2b:3b=98:2[d)]
3	1a (n=2)	EtMgCl	95	2a only[c)]
4	1b (n=1)	EtMgCl	95	2b only[c)]
5	1a (n=2)		95	2a:3a=97:3[c)]
6	1a (n=2)	PhMgBr	85	2a:3a=95:5[d)]
7	1c (n=2)	MeMgBr	91	2c:3c=60:40[c)]
8	1d (n=1)	MeMgBr	95	2d:3d=70:30[d)]

a) RMgX(5 eq.) was added to a solution of 1(0.1 mole). b) Purified by SiO_2 column chromatography. c) Determined by ^1H NMR(90 MHz, C_6D_6). d) Determined by GLC(SE-52 capillary column).

addition in this system is an unprecedented example.

The α-ketoacetals(1a-d),[2,3] readily prepared from the corresponding α-hydroxydimethylacetals,[4] reacted with methylmagnesium bromide in tetrahydrofuran at -78°C(runs 1,2,7,8). The results are summarized in the Table. Extremely high stereoselectivity was observed in the reactions in which (-)-(2S,3S)-1,4-dimethoxy-2,3-butanediol[5] was used as a chiral auxiliary(runs 1,2).[6] Similar results were also obtained in the reactions of 1a and 1b with other Grignard reagents(runs 3-6). The stereochemistry of the product from 1a in run 1 was assigned to 2a by comparing the specific rotation[7a] of the 2-hydroxy-2-methylcyclohexanone obtained from the product by acid hydrolysis(80% CF_3COOH, r.t.) with the reported value,[7b] whose result was ascertained by adopting the Horeau's method to the diols obtained by the reduction($LiAlH_4$) of the α-hydroxyketone.[8] The stereochemistries of the products in runs 2-4 and 6-8 were assigned similarly by comparing the specific rotation[7a] of the corresponding α-hydroxy-α-substituted cycloalkanones with the reported values.[7b] The product in run 5 was correlated to the product in run 3 by hydrogenation (H_2/Pd-C). The formation of the predominant products(2) can be explained by the attack of Grignard reagents on the si-face of the ketones. The appearance of high stereoselectivity in runs 1-6 would suggest the chelation of the reagent to the methoxy oxygen atom on the same side of ketone in the reactions of 1a and 1b.

It is worthy to note that the acetals, the most popular protecting group of carbonyl groups, work as chiral auxiliary in this asymmetric synthesis.

References and Notes

1 (a) W. S. Johnson, J. D. Elliott, G. J. Hanson, J. Am. Chem. Soc., 106, 1138 (1984); (b) W. S. Johnson, C. Edington, J. D. Elliott, I. R. Silverman, J. Am. Chem. Soc., 106, 7588 (1984), and references therein. J. D. Elliott, J. Steele, W. S. Johnson, Tetrahedron Lett., 26, 2535 (1985); (c) A. Ghribi, A. Alexakis, J. F. Normant, Tetrahedron Lett., 25, 3083 (1984). A. Mori, J. Fujiwara, K. Maruoka, H. Yamamoto, J. Organometal. Chem., 285, 83 (1985). J. Fujiwara, Y. Fukutani, M. Hasegawa, K. Maruoka, H. Yamamoto, J. Am. Chem. Soc., 106, 5004 (1984) and references therein. Y. Fukutani, K. Maruoka, H. Yamamoto, Tetrahedron Lett., 25, 5911 (1984); (d) M. Suzuki, Y. Kimura, S. Terashima, Chem. Lett., 1985, 367; (e) T. Matsumoto, F. Matsuda, K. Hasegawa, M. Yanagiya, Tetrahedron, 40, 2337 (1984).

2 Prepared by transacetalization with the chiral diols (p-TsOH/CH_2Cl_2/r.t.) followed by oxidation. Details of these syntheses will be published elsewhere.

3 Satisfactory spectroscopic data were obtained for all new compounds.

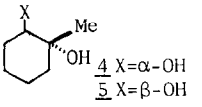
4 R. M. Moriarty, K-C Hou, Tetrahedron Lett., 25, 691 (1984).

5 Prepared from L-(+)-tartaric acid: $[\alpha]_D$ -3.95° (c 3.3, $CHCl_3$). (-)-(2R,3R)-2,3-Butanediol was purchased from Aldrich Co.

6 Poor diastereoselective alkylation reactions of 1a-d with MeLi were observed. 2a:3a=40:60; 2b:3b=50:50; 2c:3c=65:35; 2d:3d=40:60.

7 a) $[\alpha]_D$ (run): +100°(1); +27°(2); +134°(3); +94°(4); +185°(6); +19°(7); +10°(8). In case of run 6, racemization occurred slightly during acid hydrolysis. The reaction of 1a with PhLi gave the product mixture (2a:3a=30:70). b) T. Fujisawa, M. Watanabe, T. Sato, Chem. Lett., 1984, 2055.

8 A. Horeau, Tetrahedron Lett., 1961, 506. The absolute configurations of secondary alcohols of cis-diol 4 and trans-diol 5 were determined S for 4 and R for 5, and then the stereochemistry of the tertiary alcohol was deduced. Recovered α-phenylbutyric acid showed $[\alpha]_D$ -0.8° for 4 and $[\alpha]_D$ +2.5° for 5.



4 X=α-OH
5 X=β-OH

(Received in Japan 31 October 1985)