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Grignard Reactions of 4-Substituted-2-keto-1,3-dioxanes: Highly Diastereoselective Additions Controlled by a Remote Alkyl Group

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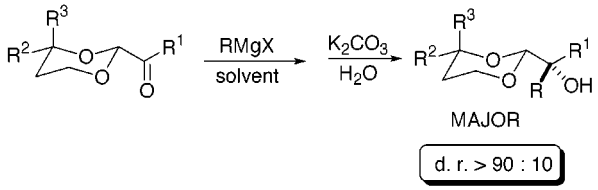
ABSTRACT



The reactions of Grignard reagents with a representative series of simple *cis*-2-keto-4-substituted-1,3-dioxanes have been investigated. The stereochemical outcome of these highly diastereoselective additions (dr > 90:10) is consonant with Cram's chelate model on the assumption that RMgX coordinates preferentially with the ring oxygen remote from the C(4) substituent.

Since the formulation of what has come to be known as "Cram's chelate rule" [1] describing the stereochemical outcome of nucleophilic addition to a chiral aldehyde or ketone bearing an α-polar substituent capable of chelation with an organometallic reagent,[2] considerable effort has been devoted to development of chiral auxiliaries incorporating such polar groups to control facial selectivity in the addition of an organometallic reagent to a carbonyl group.[3] Among the more successful approaches to chelation-controlled asymmetric induction in addition reactions of organometallic reagents are those employing various 1,3-oxathianes,[4] 1,3-oxazines,[5] or 1,3-dioxolanes derived from C_2-symmetric diols[6] as the chiral adjuvant. Somewhat surprisingly, there appear to be no reports of the use of a simple 4-substituted 1,3-dioxane as the control element in organometallic addition to a carbonyl group. Herein we disclose the results of an exploratory investigation of the reaction of Grignard reagents with *cis*-4-substituted-2-keto-1,3-dioxanes demonstrating that such addition reactions are highly diastereoselective.

Although relatively few 2-keto-1,3-dioxanes have been reported in the literature, the substrates used in the present study (Figure 1) were easily prepared by one of the two methods depicted in Scheme 1. While transacetalization,[7] illustrated for the preparation of **1**, is the more direct route, the reaction invariably affords a mixture of isomeric 2-keto-

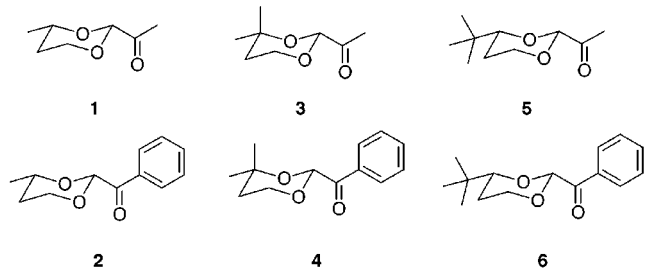


Figure 1. 2-Keto-1,3-dioxanes.

(1) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748.
(2) (a) Eliel, E. L. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2. (b) Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1990**, *112*, 6130. (c) Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462.
(3) For a recent review, see: Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191.

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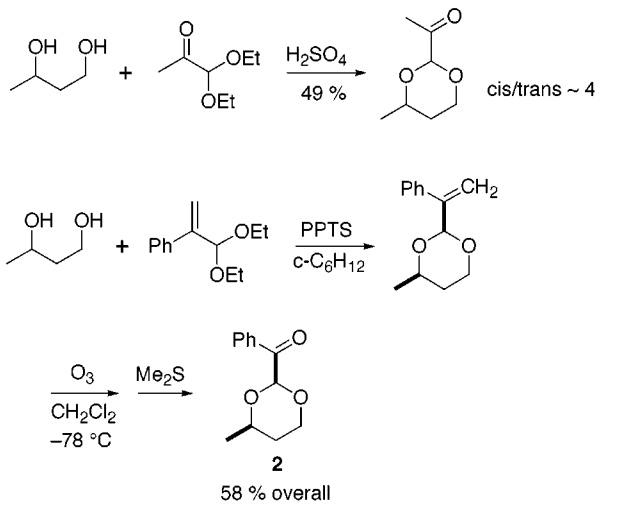
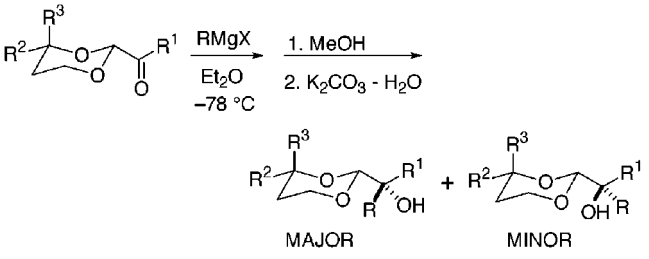
Scheme 1



4-substituted-1,3-dioxanes[8] from which the more polar cis-isomer must be isolated by chromatography. The two-step preparation of *cis*-2-keto-4-substituted-1,3-dioxanes, illustrated in Scheme 1 for the synthesis of **2**, is often the more convenient method since it provides isomerically pure material and avoids the tedious chromatographic separation.

Exploratory Grignard reactions were performed at −78 °C by addition of an excess (typically 2 equiv)[9] of the reagent to a solution of the 2-keto-1,3-dioxane (Figure 1) in dry diethyl ether. The results of these experiments are summarized in Table 1; the configuration of the diastereoisomeric tertiary alcohol products (designated major and minor in Table 1) was established as described below.

Table 1. Grignard Reactions of 4-Substituted-2-keto-1,3-dioxanes[a]



entry	ketone	R^1	R^2	R^3	RMgX	yield,[b] %	dr[c]
1	**1**	CH_3	CH_3	H	PhMgBr	84	93:7
2	**3**	CH_3	CH_3	CH_3		98	93:7
3	**5**	CH_3	*t*-Bu	H		78	91:9
4	**2**	Ph	CH_3	H	MeMgBr	86	85:15
5	**4**	Ph	CH_3	CH_3		90	84:16
6	**6**	Ph	*t*-Bu	H		80	90:10
7	**2**	Ph	CH_3	H	MeLi	78	64:36

[a] The Grignard reagent (2 molar equiv) in Et_2O was added at −78 °C to a solution of the keto-1,3-dioxane in Et_2O (0.15 M final concentration), and the resulting solution was stirred at −78 °C for 1 h before being quenched with MeOH. [b] Isolated yield of a mixture of diastereoisomers. [c] Diastereomeric ratio determined by GC analysis of TMS ethers.

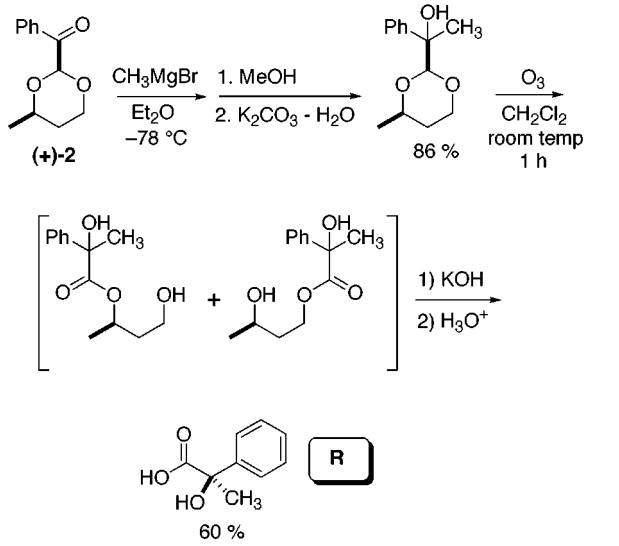
Cursory inspection of the data in Table 1 demonstrates that the additions are quite diastereoselective, particularly those involving reaction of PhMgBr with the methyl ketones **1**, **3**, or **5** (Table 1, entries 1−3). Moreover, as detailed below, the less diastereoselective reactions of MeMgBr with the phenyl ketones (Table 1, entries 4−6) are easily optimized to give dr values on the order of ∼95:5 by employing a solvent other than Et_2O as the reaction medium. It should also be noted that an organolithium reagent is much less selective in reaction with a 2-keto-1,3-dioxane than is the corresponding Grignard reagent (Table 1, cf. entries 4 and 7).

A particularly striking feature of these results is the high diastereoselectivity engendered by a single methyl substituent at C(4) in the *cis*-2-keto-4-methyl-1,3-dioxanes (**1** and **2**). Indeed, a methyl group is approximately as effective in directing facial selectivity in the addition reactions as is a much larger *t*-Bu group at this position (Table 1; cf. entries 1 and 3, cf. entries 4 and 6). In this connection, it might be noted that the isomerically homogeneous 2-keto-4,4-dimethyl-1,3-dioxanes (such as **3** and **4**) are particularly attractive substrates for facially selective Grignard reactions since they do not require separation of cis−trans isomers[8] before use.

To establish the stereochemical outcome of these facially selective additions, it is necessary to determine the configuration of the stereogenic center created in the reaction. To this end, (4*R*)-(+)-*cis*-2-benzoyl-4-methyl-1,3-dioxane [(+)-**2**] was prepared from commercially available (−)-1,3-butanediol following the two-step route depicted in Scheme 1 for the racemic material (**2**).

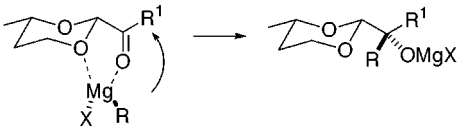
As illustrated in Scheme 2, treatment of (+)-**2** with MeMgBr under conditions identical to those used for the racemic substrate (Table 1, entry 4) gave an 85:15 mixture of diastereoisomeric alcohols. While it might seem a simple matter to reveal the latent α-hydroxy aldehyde by hydrolysis of the 1,3-dioxane, this approach was avoided. Not only are

Scheme 2



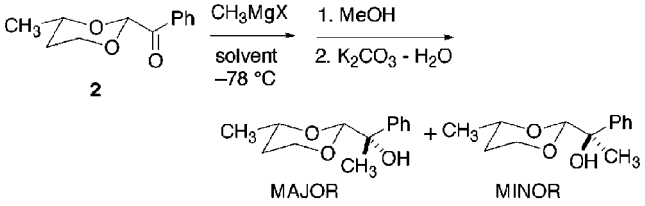
α-hydroxy aldehydes notoriously difficult to manipulate,[10] the tertiary, benzylic alcohol function is also prone to dehydration under the hydrolysis conditions. Although such considerations would seem to belie the utility of *cis*-4-substituted-1,3-dioxanes as chiral auxiliaries, the system possesses precisely the stereochemistry (an axial C(2)-H flanked by two oxygen atoms) required for facile insertion of ozone into the C(2)−H bond under neutral conditions.[11] This oxidation, developed by Deslongchamps' group,[11] was used to convert the addition products to a mixture of esters from which (−)-atrolactic acid (presumably with er = dr = 85:15) was isolated in 60% overall yield by saponification (Scheme 2); a single recrystallization afforded pure (−)-atrolactic acid.[12] Since the levorotatory acid is known to have the *R*-configuration,[13] the sense of the facial selectivity of the Grignard additions is established to be that shown in Table 1.

The stereochemistry of the Grignard addition reactions is easily rationalized, as shown below, in terms of Cram's chelate model[1,2] on the reasonable assumption that RMgX coordinates preferentially to the ring oxygen remote from the C(4) substituent. In this connection, it might be noted that similar chelation control exerted by a C(4) group has been observed in the Grignard−ortho ester reactions of *cis*-2-methoxy-4-methyl-1,3-dioxane[14] as well as in the highly regioselective acylative cleavage of 4-substituted-1,3-dioxanes.[15]



As noted above, the diastereoselectivities observed for reaction of Grignard reagents with *cis*-2-keto-4-substituted-1,3-dioxanes in Et_2O (Table 1) are not necessarily the highest possible for these addition reactions. As demonstrated by the data summarized in Table 2, solvent has a pronounced effect on the facial selectivity of the addition reaction and the nature of the halogen in the RMgX reagent has a more modest influence. Whereas addition of MeMgBr to **2** in Et_2O proceeds with moderate selectivity at −78 °C (viz. 85:15; Table 1, entry 4), the selectivity is improved significantly (dr = 95:5) when an ethereal solution of the Grignard is added to a solution of **2** in THF (Table 2, entry 3). Conversely, selectivity is eroded when reactions are run in less strongly coordinating solvents such as MTBE and (*i*-Pr)$_2$O (Table 2, entries 1 and 2). The etiology of these solvent effects may well be complex: a more poorly coordinating solvent should favor formation of the putative Cram chelate between RMgX and the dioxane[2,3] but solvent may also affect the Schlenk equilibrium and the degree of association of the Grignard reagent.

Table 2. Grignard Reactions of *cis*-2-Benzoyl-4-methyl-1,3-dioxane (**2**)[a]



entry	RMgX	solvent	yield,[b] %	dr[c]
1	MeMgBr	MTBE−Et_2O (9:1 by vol)	72	82:18
2		(i-Pr)$_2$O−Et_2O (9:1 by vol)	23[d]	79:21
3		THF−Et_2O (9:1 by vol)	90	95:5
4	MeMgCl		96	92:8
5	MeMgI		69[e]	96:4

[a] The Grignard reagent (2 molar equiv) in Et_2O was added at −78 °C to a solution of **2** in the indicated solvent (0.15 M final concentration), and the resulting solution was stirred at −78 °C for 1 h. [b] Isolated yield of a mixture of diastereoisomers. [c] Diastereomeric ratio determined by GC analysis of the TMS ethers. [d] Incomplete reaction after 1.5 h. [e] Dehydration of the alcohol products accounts for the lower yield.

In summary, the results of this preliminary investigation demonstrate for the first time that simple 4-substituted 1,3-dioxanes are effective as chiral auxiliaries for control of facial selectivity in the addition of a Grignard reagent to a ketone. The highly diastereoselective additions appear to be the result of preferential formation of a Cram-type chelate between the RMgX and the ring oxygen remote from the C(4)substituent. The ready availability of a variety of 1,3-diols for the synthesis of enantiopure *cis*-2-keto-4-substituted-1,3-dioxanes, coupled with the ease with which the adjuvant may be removed by Deslongchamps oxidation from the tertiary

(4) (a) Eliel, E. L.; Koskimies, J. K.; Lohri, B. *J. Am. Chem. Soc.* **1978**, *100*, 1614. (b) Eliel, E. L.; Koskimies, J. K.; Lohri, B.; Frazee, W. J.; Morris-Natschke, S.; Lynch, J. E.; Soai, K. In *Asymmetric Reactions and Processes in Chemistry*; Eliel, E. L., Otsuka, E., Eds.; ACS Symposium Series 185, American Chemical Society: Washington, DC, 1982; pp 37−53. (c) Frye, S. V.; Eliel, E. L. *J. Am. Chem. Soc.* **1988**, *110*, 484, and references therein.

(5) (a) He, X.-C.; Eliel, E. L. *Tetrahedron* **1987**, *43*, 4979. (b) Eliel, E. L.; He, X.-C. *J. Org. Chem.* **1990**, *55*, 2114. (c) Ko, K.-Y.; Park, J.-Y. *Tetrahedron Lett.* **1997**, *38*, 407.

(6) (a) Tamura, Y.; Ko, T.; Kondo, H.; Annoura, H.; Fuji, M.; Takeuchi, R.; Fujioka, H. *Tetrahedron Lett.* **1986**, *27*, 2117. (b) Heitz, M. P.; Gellibert, F.; Mioskowski, C. *Tetrahedron Lett.* **1986**, *27*, 3859. (c) Thiam, M.; Chastrette, F. *Bull. Chim. Soc. Fr.* **1992**, *192*, 161. (d) Akhoon, K. M.; Myles, D. C. *J. Org. Chem.* **1997**, *62*, 6041.

(7) Cho, B. T.; Chun, Y. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2095.

(8) Although the conformational energy of a 2-acetyl or 2-benzoyl group in the 1,3-dioxane system has not been determined, the low conformational free energy of a 2-CO_2Et group ($-\Delta G° = 0.92$ kcal/mol) suggests that the isomeric composition of product mixtures prepared by transacetalization may reflect the actual equilibrium ratio, see: Tschierske, C.; Köhler, H.; Zaschke, H.; Kleinpeter, E. *Tetrahedron* **1989**, *45*, 6987.

(9) It should be noted that the use of 1 equiv of RMgX gives virtually the same product composition (dr); however, yields were somewhat lower in reactions employing only 1 equiv of reagent.

(10) See, for example: Lynch, J. E.; Eliel, E. L. *J. Am. Chem. Soc.* **1984**, *106*, 2943.

(11) (a) Deslongchamps, P.; Moreau, C. *Can. J. Chem.* **1971**, *49*, 2565. (b) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983; pp 41−47.

(12) Mp 112−114 °C (lit.[13] mp 114−116 °C); $[\alpha]^{24}_D = -36.3$ [*c* 3.43, EtOH] (lit.[13] $[\alpha]^{13.8}_D = -37.7$ [*c* 3.4, EtOH].

(13) McKenzie, A.; Clough, G. W. *J. Chem. Soc.* **1910**, *97*, 1016.

(14) Bailey, W. F.; Croteau, A. A.; Rivera, A. D. *Tetrahedron Lett.* **1997**, *38*, 4047.

(15) (a) Bailey, W. F.; Rivera, A. D. *J. Org. Chem.* **1984**, *49*, 4958. (b) Bailey, W. F.; Zarcone, L. M. J.; Rivera, A. D. *J. Org. Chem.* **1995**, *60*, 2532.

carbinol center created in the Grignard reaction (Scheme 2), suggests that this system may be of significant practical value for the asymmetric synthesis of enantiomerically pure α-hydroxy acids. We are actively investigating this possibility.

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Supporting Information Available: Detailed experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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