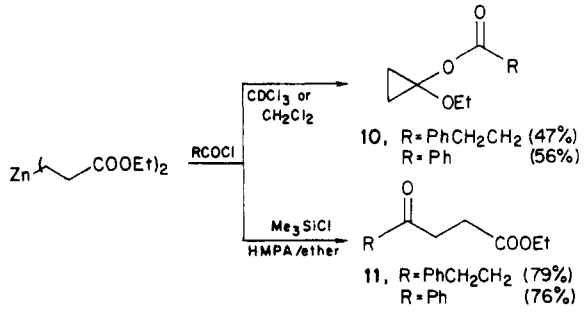
vastly accelerates the reaction of the homoenolate **2** with aldehydes in halomethane (note that $ZnCl_2$ is ineffective) provides a vital support for our proposal which involves activation of the carbonyl group by Me_3SiCl (cf. **9**).[11] The higher Lewis acidity of Me_3SiI,[12] as compared with Me_3SiCl, explains the wider tolerance of the electrophiles (vide supra) in the ZnI_2-catalyzed reaction.

Since the catalytic reaction with acid chlorides tended to give complex results, stoichiometric conditions were examined. To our surprise, the purified homoenolate **2** in $CDCl_3$ reacted with acid chlorides *exclusively on oxygen* to produce the 1-(acyloxy)cyclopropanes **10** in good yield. The characteristic NMR signals of the cyclopropane protons[13] were diagnostic for identification of these structurally interesting products.

In more polar (and basic) solvents (e.g., in ether) consumption of the reactants almost stopped; with 2 equiv of HMPA, however, the reaction again proceeded as fast as in $CDCl_3$ but now *gave only a C-acylated product*. Thus, under the optimized conditions with 2 equiv each of Me_3SiCl and HMPA in ether, keto esters **11** were obtained in 70–80% yield.[14]



After more than 20 years since the recognition of the homoenolate chemistry[15a] the nature of the homoenolate anion still remains rather obscure.[15b] The condition-dependent C/O-dichotomy of the homoenolate reported above is, therefore, of great heuristic value, showing that homoenolate does show typical ambident reactivities related to the one widely found for enolates.

Acknowledgment. We thank Toray Silicone for the generous supply of Me_3SiCl and the Ministry of Education, Culture, and Science for the financial support.

Registry No. **3**, 27374-25-0; **4** (R^1 = H, R^2 = Ph), 87768-37-4; **4** (R^1 = H, R^2 = PhCH=CH), 96790-96-4; **4** (R^1 = H, R^2 = CH_3CH=CH), 96759-95-4; **4** (R^1 = H, R^2 = benzodioxol-5-yl), 96759-96-5; **4** (R^1 = H, R^2 = *p*-$NO_2C_6H_4$), 96759-97-6; **4** (R^1 = H, R^2 = $CH_3(CH_2)_5$), 96759-98-7; **4** (R^1 = CH_3, R^2 = Ph), 96790-97-5; **5**, 96760-00-8; **7**, 96760-01-9; **8** (R = Ph), 96760-02-0; **10** (R = $Ph(CH_2)_2$), 96760-03-1; **10** (R = Ph), 91496-66-1; **11** (R = $Ph(CH_2)_2$), 90147-73-2; **11** (R = Ph), 6270-17-3; PhCHO, 100-52-7; PhCH=CHCHO, 104-55-2; CH_3CH=CHCHO, 4170-30-3; *p*-$NO_2C_6H_4CHO$, 555-16-8; $CH_3(CH_2)_5CHO$, 111-71-7; $PhC(O)CH_3$, 98-86-2; $PhCH(OMe)_2$, 1125-88-8; ZnI_2, 10139-47-6; $ZnCl_2$, 7646-85-7; $PhCH_2OCH(CHO)(CH_2)_4CH_3$, 96759-99-8; $Zn((CH_2)_2C(O)OEt)_2$, 90147-62-9; $Ph(CH_2)_2C(O)Cl$, 645-45-4; PhC(O)Cl, 98-88-4; piperonal, 120-57-0.

(11) For recent proposals of a related role of Me_3SiCl, see: ref 2a; RajanBabu, T. V. *J. Org. Chem.* **1984**, *49*, 2083.

(12) Cf. Sakurai, H.; Sasaki, K.; Hosomi, A. *Tetrahedron Lett.* **1981**, *22*, 745.

(13) 1-Ethoxy-1-(benzoyloxy)cyclopropane: IR (neat) 1750 (vs), 1600 (w); ^1H NMR (CCl_4) 0.75–1.0 (m, 4 H, cyclopropane), 1.05 (t, J = 7 Hz, 3 H), 2.3–3.65 (m, 2 H), 2.65–3.0 (m, 2 H), 3.44 (q, J = 7 Hz, 2 H), 6.93 (s, 5 H).

(14) Performing the reaction in the presence of Cu^+ (ref 2a) is preferred for synthetic purposes as it is faster, giving cleaner products.

(15) (a) Nickon, A.; Lambert, J. L. *J. Am. Chem. Soc.* **1962**, *84*, 4604. (b) Review: Werstiuk, N. H. *Tetrahedron* **1983**, *39*, 205.

(16) Spectral studies indicated that **2** does not change its structure in all solvents used for the chemical reactions. Discussion of the origin of the C/O-dichotomy will be deferred to the full report.

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Opposite High Diastereoselectivity in the Carbonyl Addition of Organolithium and Grignard Reagents to 3-Acylisoxazolines

Summary: The reactions of organolithium and Grignard reagents with 3-acyl-4,5-disubstituted-isoxazolines to produce tertiary alcohols show high but opposite diastereoselectivity; competitive pathways involving attack on s-trans and metal-chelated s-cis conformations of the O=CC=N system are proposed.

Sir: Carbonyl addition of organometallic compounds is one of the two or three most extensively used reactions for organic synthesis. Stereochemical aspects have been exhaustively studied and have been instrumental in the development of Cram's rule[1] (open-chain, cyclic, and dipolar models) and Prelog's rule.[2] It is generally perceived that organolithium and Grignard reagents add by similar mechanisms,[3] although it is also recognized that stereoselectivity can differ significantly.[1,4-5] In a few instances high metal-dependent selectivity for opposite faces has been documented.[6] The degree of metal chelation is a well-recognized powerful factor in determining the stereochemical outcome for addition where α- or β-heteroatoms are present.[7]

Carbonyl addition to the 3-acylisoxazolines[8] **1a** and **3a**

(1) For a recent review, see: Eliel, E. L. In "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol 2; pp 125–55.

(2) For a review, see: Fiaud, J. C. In "Stereochemistry, Fundamentals and Methods"; Kagan, H. B., Ed.; Georg Thieme: Stuttgart, 1977; Vol. 3; pp 20–49.

(3) Both SET and polar mechanisms appear to be involved: Liotta, D.; Saindane, M.; Waykole, L. *J. Am. Chem. Soc.* **1983**, *105*, 2922. Ashby, E. C.; Bowers, J. R., Jr. *J. Am. Chem. Soc.* **1981**, *103*, 2242 and references cited therein. Ashby, E. C. *Pure Appl. Chem.* **1980**, *52*, 545. See also: Smith, J. G.; Irwin, D. C. *J. Am. Chem. Soc.* **1980**, *102*, 2757.

(4) For three recent examples involving 1,2-asymmetric induction, see: (a) Still, W. C.; McDonald, J. H., III. *Tetrahedron Lett.* **1980**, *21*, 1031. (b) Eliel, E. L.; Morris-Natsche, S. *J. Am. Chem. Soc.* **1984**, *106*, 2937. (c) Mead, K.; Macdonald, T. L. *J. Org. Chem.* **1985**, *50*, 422.

(5) For examples involving long-range asymmetric induction, see: (a) Still, W. C.; Schneider, J. A. *Tetrahedron Lett.* **1980**, *21*, 1035 [β-alkoxy aldehydes]. (b) Lutomski, K. A.; Meyers, A. I. In "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol 3; pp 213–74 (pp 241, 47) [2-ketooxazolines and 2-acylphenyloxazolines]. (c) Whitesell, J. K.; Bhattacharya, A.; Henke, K. *J. Chem. Soc., Chem. Commun.* **1982**, 988 [α-keto esters]. (d) Fouquey, C.; Jaques, J.; Angiolini, L.; Tramontini, M. *Tetrahedron* **1974**, *30*, 2801 [β-amino ketones].

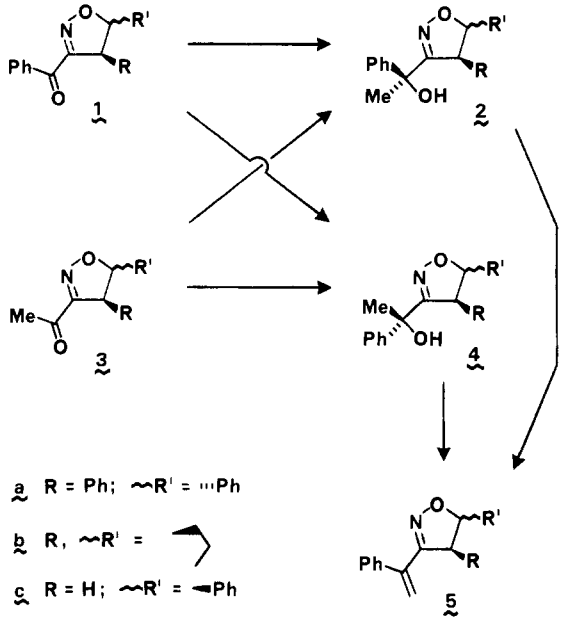
(6) We are aware of only four examples: (a) Beloeil, J.-C.; Bertranne, M.; Fetizon, M.; Prange, T. *J. Chem. Soc., Chem. Commun.* **1981**, 363 [LiC≡CH and BrMgC≡CMgBr]. (b) Stocker, J. H. *J. Am. Chem. Soc.* **1966**, *88*, 2878 [PhMgBr and PhLi]. See also: Stocker, J. H. *J. Org. Chem.* **1964**, *29*, 3593. (c) Mukaiyama, T.; Soai, K.; Sato, T.; Shimizu, H.; Suzuki, K. *J. Am. Chem. Soc.* **1979**, *101*, 1455 [chiral pyrollidine complexes of R_2Mg and RLi]. (d) Miljković, M.; Gligorijević, M.; Satoh, T.; Miljković, D. *J. Org. Chem.* **1974**, *39*, 1379 [MeMgI and MeLi].

(7) For a discussion, see: (a) ref 4b and 4c. (b) Morrison, J. D.; Mosher, H. S. "Asymmetric Organic Reactions"; Prentice-Hall: Englewood Cliffs, NJ, 1971; pp 100–108.

(8) 3-Acylisoxazolines are conveniently prepared from alkenes and α-nitro ketones under acidic conditions: Wade, P. A.; Amin, N. V.; Yen, H.-K.; Price, D. T.; Huhn, G. F. *J. Org. Chem.* **1984**, *49*, 4595.

0022-3263/85/1950-2804$01.50/0

Scheme I



a R = Ph; ~R' = ···Ph

b R, ~R' =

c R = H; ~R' = —Ph

Table I. Products of Carbonyl Addition

ketone	RM	solvent	temp, °C	products	yield, %	ratio[a]
1a	MeLi	THF	−78	**2a/4a**	94	99.5:0.5
	MeMgBr	CH_2Cl_2	−78	**2a/4a**	77	2:98
			0–5		72	3:97
		THF	0–5		49	20:80
3a	PhLi	THF	−78	**2a/4a**	82	1:99
	PhMgBr	CH_2Cl_2	−78	**2a/4a**	71	>99:1
			0–5		70	97:3
1b	MeLi	THF	−78	**2b/4b**	87	5:95
	MeMgBr	CH_2Cl_2	−78	**2b/4b**	78	93:7
1c	MeLi	THF	−78	**2c/4c**	93	41:59
	MeMgBr	CH_2Cl_2	−78	**2c/4c**	83	51:49

[a] Using a threefold excess of organometallic reagent in all cases.

has been examined with the expectation of considerable 1,3-asymmetric induction (Scheme I). These reactions proved to be higly stereoselective but surprisingly metal-dependent; organolithium reagents attacked one face of the carbonyl group while Grignard reagents attacked the opposite face (Table I). Thus, isoxazoline **1a** reacted at −78 °C with excess methyllithium in THF to give a 94% yield of the tertiary alcohols **2a** and **4a** (99.5:0.5 ratio,[9] respectively). The order of group introduction could be reversed with a concomitant reversal in diastereoselectivity; isoxazoline **3a** gave alcohols **2a** and **4a** (1:99 ratio). In sharp contrast, phenylmagnesium bromide and methylmagnesium bromide reacted with the isoxazolines **1a** and **3a** to afford the alcohols **4a** and **2a**, respectively, as the major products. Similar conditions to the organolithium reactions could be employed, but yields and stereoselectivities were optimized by using methylene chloride as solvent. The diastereomer ratios were greater than 98:2 in both cases at −78 °C, decreasing somewhat at 0–5 °C. Reaction of isoxazoline **1b** with methyllithium at −78 °C gave an 87% yield of alcohols **2b** and **4b** in a 95:5 ratio; the ratio was essentially reversed (7:93) for methylmagnesium bromide.

Alcohols **2a,b** and **4a,b** were identified from spectral and elemental analysis data;[10] **2a** and **4a** were both dehydrated

(9) Isomer ratios were determined by HPLC; qualitative confirmation was obtained by ^1H NMR and isolation techniques.

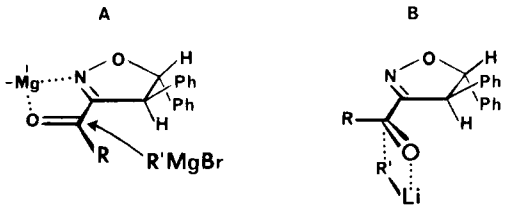


Figure 1. (A) Attack of Grignard reagents on ketones **1a** and **3a**. (B) Attack of organolithium reagents on ketones **1a** and **3a**.

under acidic conditions to alkene **5a**. However, the configurational assignment required an X-ray determination, performed on alcohol **2a**. Configurational assignments for alcohols **2b** and **4b** are based on ^1H NMR spectra; the upfield 4-H signal was assigned to alcohol **4b** by analogy to **4a**.

Diastereoselection in these reactions is due in large part to 1,3-asymmetric induction from the chiral center at the 4-position of the heterocyclic ring. Thus, isoxazoline **1c** reacted with methylmagnesium bromide to give an 83% yield of a 49:51 mixture of alcohols **2c** and **4c**. With methyllithium, there was relatively low stereoselectivity (59:41)[8] favoring the formation of alcohol **2c**. Configurational assignments were based on ^1H NMR by comparison to alcohols **2a,b**, **4a,b** and a series of *cis*- and *trans*-4,5-diphenylisoxazolines.[11]

We attribute the high stereoselectivity in the reactions of **1a**, **1b**, and **3a** to strongly biased attack on planar conformations of the O=CC=N system (Figure 1). Attack presumably occurs through a metal-chelated s-cis transition state with Grignard reagents (cf., Cram's cyclic model). The attack might be as shown; alternatively, attack might occur on a metal-chelated ketyl radical anion subsequent to electron transfer.[3] For the lithium reagents, we propose that attack occurs through a coordinated but nonchelated s-trans transition state.[12]

Registry No. **1a**, 92241-13-9; **1b**, 96791-65-0; **1c**, 7064-02-0; **2a**, 96791-63-8; **2b**, 96791-66-1; **2c**, 92241-24-2; **3a**, 96791-62-7; **4a**, 96791-64-9; **4b**, 96791-67-2; **4c**, 92241-23-1; **5a**, 96791-68-3.

Supplementary Material Available: ORTEP drawing for compound **2a** and tables of X-ray crystallographic atomic positional and thermal parameters (4 pages). Ordering information is given on any current masthead page.

(10) All new compounds gave correct (±0.4%) elemental analyses. ^1H NMR spectra ($CDCl_3$) were taken at 90 MHz. **2a**: δ 7.0–7.4 (m, 15 H), 5.46 (d, 1 H, J = 5.8 Hz), 4.17 (d, 1 H, J = 5.8 Hz), 2.89 (s, 1 H), 1.63 (s, 3 H). **2b**: δ 7.2–7.6 (m, 5 H), 5.0–5.2 (m, 1 H), 3.7–4.0 (m, 1 H), 2.73 (s, 1 H), 1.84 (s) on 1.2–2.2 (m) [9 H total]. **4a**: δ 7.0–7.4 (m, 15 H), 5.40 (d, 1 H, J = 5.0 Hz), 3.97 (d, 1 H, J = 5.0 Hz), 2.07 (s, 1 H), 1.78 (s, 3 H). **4b**: δ 7.2–7.6 (m, 5 H), 4.9–5.1 (m, 1 H), 3.2–3.5 (m, 1 H), 2.73 (s, 1 H), 1.87 (s) on 1.3–2.2 (m) [9 H total].

(11) From 3-substituted *cis*- and *trans*-4,5-dihydro-4,5-diphenylisoxazoles it is clear that a 4-H located cis to a 5-phenyl group is 0.2–0.3 ppm upfield from a 4-H located trans, presumably due to shielding of the cis-H (for example, cf., spectra for **6e** and **6f** in: Wade, P. A.; Yen, H.-K.; Hardinger, S. A.; Pillay, M. K.; Amin, N. V.; Vail, P. D.; Morrow, S. D. *J. Org. Chem.* **1983**, *48*, 1796).

(12) The preferred nonchelated ground-state conformation of the acylisoxazoline is expected to be s-trans, by analogy to open-chain systems: Baas, P.; Cerfontain, H. *J. Chem. Soc., Perkin Trans. 2* **1979**, 151. Baas, P.; Cerfontain, H. *Ibid.* **1977**, 1351.

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