Allene-Directed Diastereoselection. Additions to Chiral Allenyl Aldehydes and Ketones

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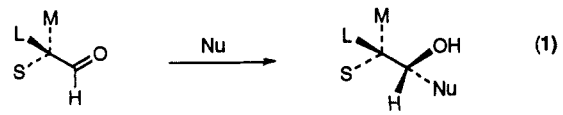
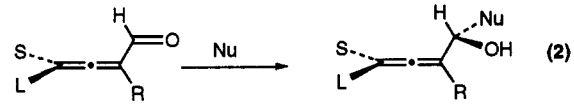
Summary: Additions of Grignard reagents and L-Selectride (Aldrich) to allenyl aldehydes and ketones DPS(R)C=C=C(R)CHO and DPS(R)C=C=C(R)$COCH_3$ occur anti to the DPS substituent.

One of the major achievements of contemporary organic synthesis has been the development of highly stereoselective routes to complex acyclic substances containing multiple stereocenters. Strategies, based on "Cram's rule" or chelation control, in which the facial preference of nucleophilic addition to an aldehyde or ketone is influenced by an adjacent stereocenter, have been successfully employed in a wide range of situations (eq 1).[1] We were



I; S = small, L = large, M = medium II (major)

interested in the analogous stereochemical directing effect of a chiral allenyl substituent on nucleophilic additions to carbonyl groups as exemplified by **III** → **IV** (eq 2).[2]

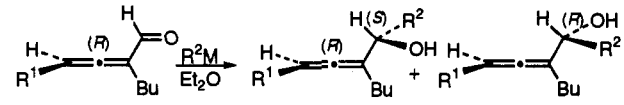


III; S = small, L = large IV (major)

Assuming a preferential s-trans transition state orientation of the allenal **III**, the nucleophilic reagent would expectedly approach the carbonyl carbon on a trajectory that is roughly parallel to the C–S or C–L bond of the allene. However, because of the greater distance between the carbonyl center and the L and S groups in **III** *vs* **I**, the magnitude of the directing effect would expectedly be less. In order to evaluate the possible applicability of such an effect for diastereoselective synthesis, we have conducted some preliminary studies which we now disclose.

For our prototype system we chose the nonracemic (*R*)-allenal **5a** in which facial access to the carbonyl is determined by *t*-Bu *vs* H. The synthesis of **5a** entailed straightforward Still [2,3]Wittig rearrangement of the (*R*)-propargylic ether **3a**[3] and subsequent Swern oxidation of the allenylcarbinol **4a** (eq 3). Treatment of aldehyde **5a** with MeMgBr in ether at −78 °C led to a 55:45 mixture of anti and syn adducts **6a** and **7a** (Table I). When *i*-PrMgBr was employed, this ratio improved to 81:19. The racemic *n*-hexylallenal **5b** afforded a 1:1 mixture of adducts **6c** and **7c** with *i*-PrMgBr as did the racemic (benzyloxy)-methyl analogue **5c**.

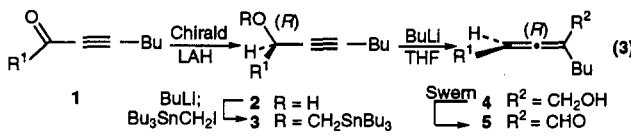
Table I. Addition of Grignard Reagents to Allenals 5a–c



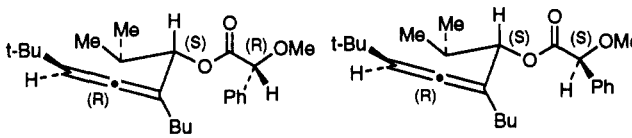
5 **6 (anti)** **7 (syn)**

R^1	5 (series)	R^2M	yield, %	6:7	series
t-Bu[a]	**a**	MeLi	95	55:45	**a**
t-Bu[a]	**a**	*i*-PrMgBr	90	81:19	**b**
C_6H_{13}[b]	**b**	*i*-PrMgBr	82	50:50	**c**
CH_2OBn[b]	**c**	MeMgBr	90	50:50	**d**
CH_2OBn[b]	**c**	*i*-PrMgBr	90	50:50	**e**

[a] ee 88%. [b] Racemic.



The stereochemistry of allenylcarbinols **6b** and **7b** was deduced from the ^1H NMR spectra of the derived (*R*)- and (*S*)-*O*-methyl mandelates.[3,4] The isopropyl methyl signals of the major (*R*)-mandelate **8** appeared at 0.62–0.67 ppm compared to 0.82–0.88 ppm for the corresponding signals of the (*S*)-mandelate **9**. In contrast, the (*R*)-mandelate of the minor (*R*)-alcohol **7b** gave rise to peaks at 0.82–0.88 ppm *vs* 0.54–0.67 ppm for the isopropyl methyls of the (*S*)-mandelate of **7b**.



8 δ *i*-Pr = 0.62 - 0.67 ppm **9** δ *i*-Pr = 0.82 - 0.88 ppm

These experiments served to validate our basic premise, but a more effective directing group was clearly needed. After some unsuccessful attempts at chelation-controlled addition, we turned to the racemic DPS (*t*-BuPh_2Si) substituted allenals **12**. Such systems are readily prepared

(1) Reviews: Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 1. Heathcock, C. H. *Ibid.* Vol. 3, Chapter 2. Eliel, E. L. *Ibid.* Vol. 2, Chapter 5.

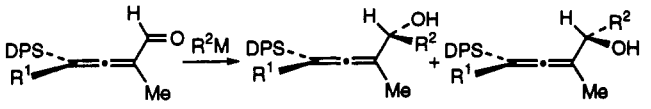
(2) Previous studies along these lines include (a) chiral vinylallenes as stereochemical directing groups in Diels–Alder additions (Reich, H. J.; Eisenhart, E. K.; Whipple, W. L.; Kelly, M. J. *J. Am. Chem. Soc.* **1988**, *110*, 6432. Curtin, M. L.; Okamura, W. H. *J. Org. Chem.* **1990**, *55*, 5278); (b) electrophilic additions to chiral allenyl enolates (Arndt, S.; Handke, G.; Krause, N. *Chem. Ber.* **1993**, *126*, 251); and (c) addition of allenylmetallics to aldehydes (Marshall, J. A.; Wang, X.-j. *J. Org. Chem.* **1992**, *57*, 1242. Danheiser, R. L.; Carini, D. J.; Kwasigroch, C. A. *J. Org. Chem.* **1986**, *51*, 3870. Yamamoto, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.-in-Chief; Pergamon Press: Oxford, 1991; Vol. 2, Heathcock, C. H., Ed.; Chapter 1.3. Stereoelectronic factors play a major role in these latter additions.

(3) *Cf.* Marshall, J. A.; Robinson, E. D.; Zapata, A. *J. Org. Chem.* **1989**, *54*, 5854. Marshall, J. A.; Wang, X.-j. *J. Org. Chem.* **1991**, *56*, 4913.

(4) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. D.; Balkovic, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. D. *J. Org. Chem.* **1986**, *51*, 2370.

0022-3263/93/1958-3233$04.00/0

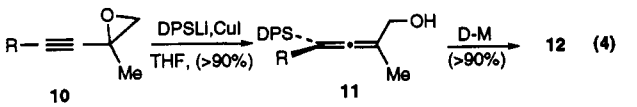
Table II. Addition of Grignard Reagents to Racemic DPS Allenal 12



12 13 14

entry	R^1	series	R^2M	yield, %	13:14	series
1	Me	a	MeMgBr	90	96:4	a
2	Me	a	MeLi	97	99:1	a
3	Me	a	EtMgBr	90	99:1	b
4	Me	a	*i*-BuMgBr	90	99:1	c
5	$MOMOCH_2$	b	MeMgBr	92	90:10	d
6	Bu	c	MeMgBr	95	83:17	e
7	Bu	c	EtMgBr	92	93:7	f
8	Bu	c	*i*-BuMgBr	90	99:1	g

through S_N2' addition of DPS cuprates to alkynyloxiranes **10**[5] and subsequent Dess–Martin oxidation (eq 4).[6]



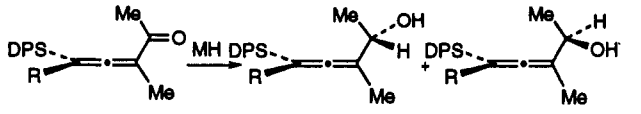
10 11 12 (4)

DPS proved to be an extremely effective directing group as can be seen from the additions summarized in Table II. Even MeMgBr adds with high diastereoselectivity (entries 1, 5, and 6). As expected, selectivity decreases as the size of R^1 increases (compare entries 1, R^1 = Me, and 5, R^1 = $MOMOCH_2$, with 6, R^1 = Bu). Even in this latter case, excellent selectivity is realized with the bulkier reagents EtMgBr and *i*-BuMgBr (entries 3, 4, 7 and 8). Interestingly, MeLi shows higher diastereoselectivity than MeMgBr (entry 1 *vs* 2).

We also examined reduction of the methyl allenyl ketones **15a–c** with DIBAH and L-Selectride (Table III). The latter proved to be the reagent of choice. The major reduction products **14a, d,** and **e** were identical with the minor products from the addition of CH_3MgBr to aldehydes **12a–c**. Once again, selectivity decreased with increasing size of the R substituent in **15** (entry 1 and 3 *vs* 5).

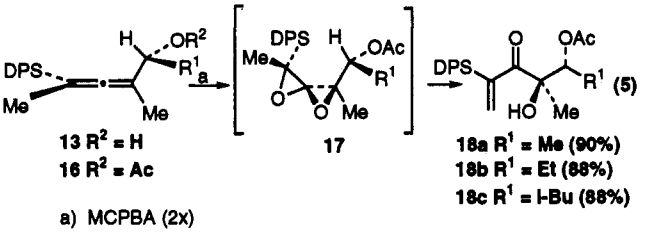
An additional example of allene directed stereocontrol is illustrated by the conversion of acetates **16a–c** to enones **18a–c** through treatment with excess *m*-CPBA (eq 5).[7] This reaction is thought to proceed *via* the bis-epoxide **17**.[8] Presumably, the double bond adjacent to the acetate is epoxidized before the silyl-substituted double bond. However, either way, the DPS would expectedly serve as an effective steric directing group in accord with the results. Enones such as **18** are potential intermediates for the synthesis of macrolide natural products.[9] Additional applications of this chemistry with nonracemic allenyl systems are currently under investigation.

Table III. Reduction of Racemic Allenyl Ketone 15



15 14 13

entry	R	series	MH	yield, %	14:13	series
1	Me	a	L-Selectride	92	99:1	a
2	Me	a	DIBAH	90	50:50	a
3	$MOMOCH_2$	b	L-Selectride	80	99:1	d
4	$MOMOCH_2$	b	DIBAH	85	50:50	d
5	Bu	c	L-Selectride	90	84:16	e



13 R^2 = H
16 R^2 = Ac
a) MCPBA (2x)
17
18a R^1 = Me (90%)
18b R^1 = Et (88%)
18c R^1 = i-Bu (88%)

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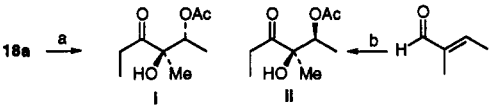
Supplementary Material Available: Experimental procedures and selected ^1H NMR spectra (56 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(5) *Cf.* Cuadrado, P.; González, A. M.; González, B.; Pulido, F. J. *Synth. Commun.* **1989**, *19*, 275. Fleming, I.; Terrett, N. K. *Tetrahedron Lett.* **1983**, *24*, 4151.

(6) Dess, P. M.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156.

(7) The stereochemistry of enone **18a** was ascertained by conversion to the ketone **i** and comparison with the diastereomer **ii** prepared from tiglic aldehyde.



a) H_2/Pd-C ; TBAF, THF b) EtMgBr ; Swern ; OsO_4, NMO; Ac_2O, py

(8) *Cf.* Crandall, J. K.; Woodrow, W. W.; Komin, J. B.; Machleder, W. H. *J. Org. Chem.* **1974**, *39*, 1723. Chan, T. H.; Ong, B. S. *Tetrahedron* **1980**, *36*, 2269.

(9) Boeckman, R. K., Jr.; Goldstein, S. W. In *The Total Synthesis of Natural Products*; Ap Simon, J., Ed.; John Wiley and Sons: New York, 1988; Vol. 7, Chapter 1.