Tetrahedron Letters,Vol.29,No.4,pp 439-442,1988
Printed in Great Britain

0040-4039/88 $3.00 + .00
Pergamon Journals Ltd.

CUPRATE ADDITIONS TO 5-METHOXYCYCLOPENTENONES: A NOVEL STEREOELECTRONIC EFFECT

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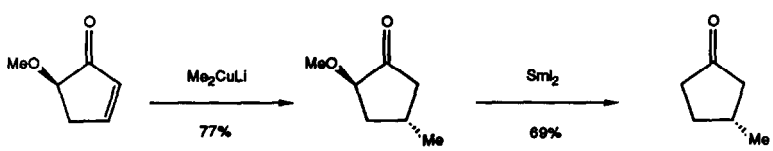
Summary: Cuprate additions to 5-methoxy-2-cyclopentenone have been found to proceed with moderate to extremely high diastereofacial selectivity, depending upon the specific cuprate and reaction protocol employed. Comparisons with related 5-substituted cyclopentenones suggest that the observed selectivity is not simply steric in nature, but instead reflects a novel stereoelectronic effect.

In connection with an ongoing synthetic program, we required that a carbon nucleophile, preferably in the form of a cuprate, undergo conjugate addition to 5-methoxy-2-cyclopentenone (1) to afford the product wherein the resultant substituents are disposed trans on the five-membered ring. This would require the existing C(5)-stereogenic center to serve as the control element. Although there are numerous examples of cuprate additions to 4-alkoxy-2-cyclopentenones, which proceed with excellent trans diastereoselection,[3] stereochemical control in a 1,3-sense has little precedent.[4] Indeed, examination of molecular models suggested it unlikely that a substituent at C(5) would exert a pronounced steric influence. These considerations notwithstanding, we have investigated the conjugate-addition of a variety of cuprates to 5-substituted cyclopentenones; we report here that moderate to very high diastereoselectivity is possible.

We initiated the study with R-5-methoxy-2-cyclopentenone (1).[5a,b] Given the propensity of cyclopentenone derivatives to undergo enolization,[6] the homochiral form of 1 was selected to permit rigorous determination of the reaction diasteroselectivity.[7] Treatment with Me_2CuLi in THF at -78° C for 30 min led predominately to the trans adduct 2; the ratio was 53:1 (capillary GC). The stereochemical outcome was demonstrated unequivocally by reductive elimination (SmI_2, THF, 69%)[8] of the methoxy group in 2 to yield known R-3-methylcyclopentanone 3.[9]



1 2 3

Intrigued by this unexpected selectivity, and aware of the sensitivity conjugate additions display to reaction conditions, we examined a variety of cuprates and reaction protocols. We were particularly cognizant of Corey's recent results, wherein the in situ use of TMSCl leads to a complete reversal of the facial selectivity observed upon additions to a γ-alkoxycyclohexenone.[10] Corey attributed the reversal to the ability of TMSCl to trap the initially formed cuprate-enone complex, thereby suppressing equilibration of the diastereomeric complexes. In view of this observation we

also explored the in situ use of TMSCl. Our results are outlined in Table I.[5]

In the case of 5-methoxycyclopentenone, the selectivity was qualitatively similar (i.e., high trans diastereoselection) not only for Me_2CuLi and Me_2CuLi/TMSCl, but also for the higher order cuprate, $Me_2Cu(CN)Li_2$,[11] and for LiI-free Me_2CuLi,[12] both in the presence or absence of TMSCl. High trans diastereoselectivity[5c] was also observed for the additions of n-Bu_2CuLi, Ph_2CuLi and the $(CH_2{=}CH)_2CuMgBr$ to 5-methoxycyclopentenone, again with and without in situ TMSCl.[5c] That higher trans selectivity was observed in most cases in the absence of TMSCl however is noteworthy.

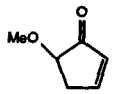
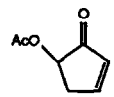
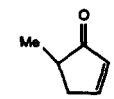
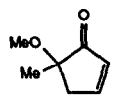
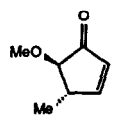
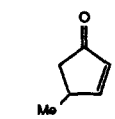
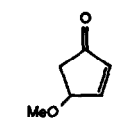
To gain further insight into the nature of this selectivity, 5-acetoxy and 5-methylcyclopentenone[5b] were prepared and reacted with Me_2CuLi and $Me_2Cu(CN)Li_2$, again with and without added TMSCl. In the case of 5-acetoxycyclopentenone, modest cis-selectivity (2.2:1 and 1.4:1)[5c] was observed with both cuprates, while 5-methylcyclopentenone somewhat surprisingly displayed modest trans-selectivity (1.9:1 and 1.6:1),[5c] again with both cuprates. Interestingly, with in situ TMSCl a reversal to trans-selectivity occurred in the case of 5-acetoxycyclopentenone with both cuprates, while with 5-methylcyclopentenone a significant increase in trans-selectivity was observed.

Several conclusions can be drawn at this point. First, steric effects do play a modest role in these additions. Note the 1.9:1 and 3.5:1 ratio of diastereomers respectively produced in the conjugate addition of Me_2CuLi and Me_2CuLi/TMSCl to 5-methylcyclopentenone. Second, the high degree of selectivity observed with 5-methoxycyclopentenone, in conjunction with the relative steric demand of the three substituents [i.e., A values: Me > OAc = OMe],[13] suggests that the methoxy group exerts its directing effect by some means other than a simple steric effect. Several explanations would seem feasible. The first is stereoelectronic in nature. A lone pair of electrons on the ether oxygen could interact with the π-system of the enone, effectively making the face opposite the methoxy group more susceptible to cuprate addition. Another possibility would be an electrostatic repulsion between the oxygen lone pairs and the electron-rich cuprate reagent.[14] In either case, the decrease in selectivity observed with 5-acetoxycyclopentenone relative to 5-methoxycyclopentenone would then be attributed to the electronic difference between the acetoxy and methoxy groups. The observed diastereoselectivity could also arise via chelation of a lithium ion with the oxygens of the methoxy and carbonyl groups to yield a reactive intermediate possessing the lithio[3.3.0]bicyclooctane skeleton. Attack from the least hindered exo face would then lead to the observed trans adducts. While difficult to exclude completely, the latter explication appears less likely given that reaction of 1 with LiI-free Me_2CuLi/TMSCl, albeit complicated by the formation of by-products, leads predominately to the trans adduct.

To explore the magnitude of the methoxy directing effect, we prepared two disubstituted cyclopentenones wherein the directing effect of the methoxy group would compete with the steric effect of a neighboring methyl group. The first substrate, 5-methyl-5-methoxycyclopentenone,[5b] was selected to minimize the steric bias upon cuprate approach to the π-system of the enone. Treatment with Me_2CuLi and $Me_2Cu(CN)Li_2$ afforded respectively a 38:1 and 30:1 mixture, wherein addition trans to the methoxy group predominated.[5b] Although the ratios were significantly lower in the presence of TMSCl, trans addition predominated in all four reactions.

The second substrate, trans-4-methyl-5-methoxycyclopentenone,[5b] was chosen in order to compete the directing ability of the 5-methoxy group with the known trans directing effect of C(4)-substituents in simple cyclopentenones (cf. Entries 12 and 13, Table 1).[3] In this case both Me_2CuLi/TMSCl and $Me_2Cu(CN)Li_2$/TMSCl afforded diastereomeric mixtures in which the major product resulted from conjugate addition trans to the methoxy group and cis to the methyl group;[5c] the ratios were 4.8:1 and 1.7:1. Here the directing ability of the C(5)-methoxy group dramatically overrides the steric effect of the C(4)-methyl group. In the absence of TMSCl however the major product in both cases was the cis-

TABLE 1. CUPRATE ADDITIONS TO CYCLOPENTENONES.

Substrate	Conditions[1]	Ratio(trans/cis)[2]	Yield
1 	a	53:1	77%
	b	34:1	76%
	c	56:1	76%
	d	4.3:1	55%
	e	13:1	81%
	f	10:1	86%
	g	7.3:1	90%
	h	4.5:1	94%
	i	32:1	72%
	j	44:1	81%
	k	17:1	22%
	l	24:1	33%
	m	32:1	14%
4 	a	1:2.2	47%
	b	5.6:1	73%
	c	1:1.4	54%
	d	12:1	72%
5 	a	1.9:1	56%
	b	3.5:1	74%
	c	1.6:1	50%
	d	3:1	73%
6 	a	38:1	61%
	b	5.5:1	63%
	c	30:1	80%
	d	4.9:1	60%
10 	a	1:3.5	59%
	b	4.8:1	77%
	c	1:2.8	59%
	d	1.7:1	49%
12 	a	>100:1	36%
	b	7:1	70%
	c	43:1	69%
	d	8:1	67%
13 	a	42:1	47%
	b	74:1	61%
	c	19:1	56%
	d	25:1	58%

[1]*Unless otherwise noted, all reactions were run at -78°C for 30 min., using 2 eq of cuprate.*

a) Me_2CuLi, THF.
b) Me_2CuLi, TMSCl (5 eq), THF , then TBAF, 1 min.
c) $Me_2Cu(CN)Li_2$, THF.
d) $Me_2Cu(CN)Li_2$, TMSCl (5 eq), THF, then TBAF, 1 min.
e) n-Bu_2CuLi, THF.
f) n-Bu_2CuLi, TMSCl (5 eq), THF, then TBAF, 1 min.
g) Ph_2CuLi, THF, -20°C.
h) Ph_2CuLi, TMSCl (5 eq), THF, -20°C, then TBAF, 1 min.
i) $(CH_2{=}CH)_2CuMgBr$, THF.
j) $(CH_2{=}CH)_2CuMgBr$, TMSCl (5 eq), THF.
k) Me_2CuLi, Et_2O.
l) Me_2CuLi-LiI free, Et_2O.
m) Me_2CuLi-LiI free, TMSCl (5 eq), THF, then TBAF, 1 min.

[2]For compounds 6 and 10, the ratio is trans or cis to methoxy.

adduct. The latter results would appear to be a reflection of the very high diastereoselectivity observed in the absence of TMSCl with Me_2CuLi and $Me_2Cu(CN)Li_2$ in the case of 4-methylcyclopentenone.

In conclusion, conjugate addition of organocuprates to 5-substituted cyclopentenones proceeds with modest to high stereoselectivity. In the case of 5-methoxy substituted cyclopentenones, the high trans selectivity is suggested to arise from either an electrostatic or stereoelectronic effect. For a theoretical discussion in support of the latter possibility, see the accompanying Letter.[15]

Acknowledgements. Support for this investigation was provided by the National Institutes of Health (National Cancer Institute) through grant CA-19033. In addition, we thank Mr. Tom Rano for help with the vinyl cuprate reaction.

1. a) Camille and Henry Dreyfus Teacher-Scholar, 1978-1983, NIH Career Development Awardee, 1980-1985, and J. S. Guggenheim Foundation Fellow, 1985-1986;

2. NIH NRSA Postdoctoral Fellow, 1985-1986.

3. Control in the 1,2-sense has been attribituted to steric and stereoelectronic factors; see Alvarez, F. S.; Wren, D.; Prince, A. J. Am. Chem. Soc. 1972, 94, 7823; Sih, C. J.; Salomon, R. G.; Price, P.; Sood, R.; Peruzotti, G. J. Am. Chem. Soc., 1975, 97, 857; Kluge, A. F.; Untch, K. G.; Fried, J. H. J. Am. Chem. Soc., 1972, 94, 7827; Stork, G.; Isobe, M. J. Am. Chem. Soc., 1975, 97, 6260; Roush, W. R., Lesur, B. M. Tetrahedron Lett., 1983, 24, 2231; Ibuka, T. Tetrahedron Lett., 1980, 21, 4073.

4. For an example of 1,3-stereoselection see: Caton, M. P. L.; Darnbrough, G.; Parker, T.; Peart, B J.; Podmore, M. L.; Threlfall, T. L. J. Chem. Soc., Perkin I, 1983, 319.

5. (a) The struture assigned to each new compound was in accord with its infrared and ^1H NMR (250 or 500 MHz) spectra, as well as elemental composition data [HRMS (parent ion identification) and/or combustion analysis (± 0.4%)]. (b) Preparation of the substrate cyclopentenones (1, 4-10) will by described in detail in our full account of this work. (c) Stereochemical assignments were derived either via chemical correlation with known materials or via extensive ^1H and ^{13}C NMR experiments. (d) In general best results were obtained with THF as solvent.

6. Buhler, J. D. J. Org. Chem., 1973, 38, 904; also see: Smith, A. B. III; Jerris, P. J. J. Org. Chem., 1982, 47, 1845.

7. Resolution of 5-methoxycyclopentenone was accomplished via the Johnson sulfoximine protocol; Johnson, C. R., Zeller, J. R. Tetrahedron, 1984, 40, 1225. The enantiomeric purity was estimated to be >98% ee; the absolute stereochemistry was established via X-ray analysis of an intermediate sulfoximine adduct.

8. Girard, P.; Namy, J. L.; Kagan, H. B. J. Am. Chem. Soc., 1980, 102, 2693; Molander, G. A.; Hahn, G. J. Org. Chem., 1986, 51, 1135.

9. The enantiomeric purity of 3 was >98%; Kokke, W. C. M. C., Varkevisser, F. A. J. Org. Chem., 1974, 39, 1535.

10. Corey, E. J.; Boaz, N. Tetrahedron Lett., 1985, 26, 6015.

11. Lipshutz, B. L.; Kozlowski, J. A.; Wilhelm, R. S. J. Org. Chem., 1984, 49, 3943.

12. House, H. O.; Fischer, W. F. J. Org. Chem., 1968, 33, 949.

13. Eliel, E.L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. Conformational Analysis, Wiley, 1965.

14. This possibility was suggested by unpublished results of A. R. Chamberlin and W. Hehre; also see Kahn, S. D.; Hehre, W. J. Am. Chem. Soc., 1986, 108, 7399; Vedejs, E.; McClure, C. K. J. Am. Chem Soc., 1986, 108, 1094. We thank Professor Chamberlin for communicating this information prior to publication.

15. Smith, A. B. III; Trumper, P. K. Tetrahedron Letters (Accompanying Letter).

(Received in USA 18 September 1987)