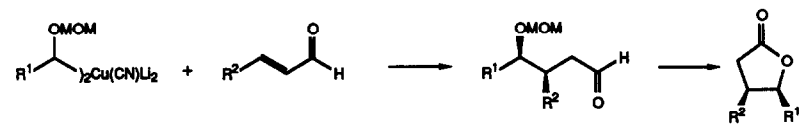
Tetrahedron Letters,Vol.29,No.32,pp 3911-3914,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

Highly Selective Syn Acyclic Homoaldol Chemistry
Synthesis of cis-3,4-Disubstituted Butyrolactones

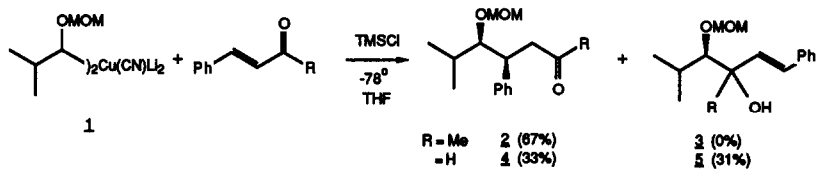
Russell J. Linderman* and Joyce R. McKenzie,
Department of Chemistry, North Carolina State University, Raleigh, NC 27695-8204

Summary Syn acyclic homoaldol products have been prepared by the conjugate addition reaction of α-alkoxyorganocuprates to enals. Selectivities of up to >250:1 have been obtained.

Acyclic homoenolate chemistry has been well studied[1] and significant results such as condensation reactions with optically active homoenolate equivalents[2] have recently been obtained. However, in contrast to the well documented aldol reaction[3], syn selectivity in homoaldol chemistry still remains a challenge. Hoppe has extensively studied α-alkoxyallyl anions as homoenolate equivalents[4], and has recently extended this approach to the selective preparation of syn homoaldol products[5]. As part of our investigations into the diastereoselective reactions of α-heteroatom substituted organocuprates, we would like to report our results on the application of α-alkoxyorganocuprates to syn selective homoaldol chemistry, and the synthesis of cis-3,4-disubstituted butyrolactones.



α-Alkoxyorganocuprates provide an alternative approach to this problem in that an equivalent to a β-cationic carbonyl compound is employed in the homoaldol reaction rather than a β-anionic carbonyl equivalent. This methodology has provided the first regiospecific synthesis of cyclic homoaldol products[6], and is readily extended to acyclic enones. However, regioselectivity problems are encountered in additions of α-alkoxyorganocuprates to enals. Addition of 1 to benzylidene acetone, in the presence of in-situ trimethylsilyl chloride (TMSCl)[7] provided a 67% yield of the 1,4-addition product 2 with no trace of the 1,2-addition product 3. Under the same reaction conditions, 1 and cinnamaldehyde provided a 50:50 regiochemical mixture of 1,4- and 1,2-addition products, 4 and 5 respectively. The result was not surprising considering that a relatively bulky α-substituted organocuprate was reacting with a β-aryl-substituted enal[8].



In contrast to the regioselectivity, the diastereoselectivity for the 1,4-addition product, as determined by capillary GC analysis of the crude reaction product, was very high, nearly 100:1. Although less reactive cuprate species did provide an improved regioselectivity, the yield of 1,4-addition product obtained was substantially reduced. We ultimately determined that enhanced regioselectivity and improved yields of 1,4-adduct could be obtained, without compromising the high diastereoselectivity observed, by a modification of the TMSCl mediated cuprate addition procedure[6,7]. By first combining TMSCl with the cuprate reagent, and then adding pre-mixed enal/TMSCl (i.e. TMSCl in-situ for both reactants prior to combination), the yield of 1,4 product increased from 33% to 46%. This observation proved to be consistent in that improved yields of the conjugate addition product were obtained in the reaction of several α-alkoxyorganocuprates and enals. Some representative yields are given in Table I. More significantly, the diastereoselectivity of the conjugate addition reaction ranged from very good, 45:1, to excellent, >250:1. Some variation in the diastereoselectivity was noted and has been attributed to partial decomposition of the cuprate species[6]. In each example, the optimal selectivity

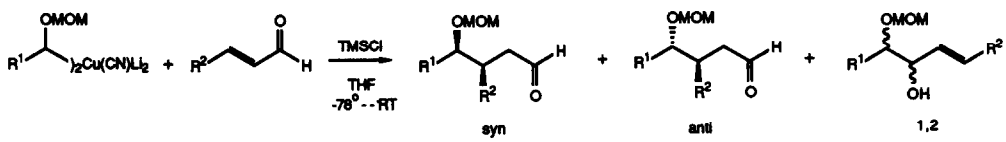


Table I Diastereoselective Additions of α-Alkoxyorganocuprates to Enal

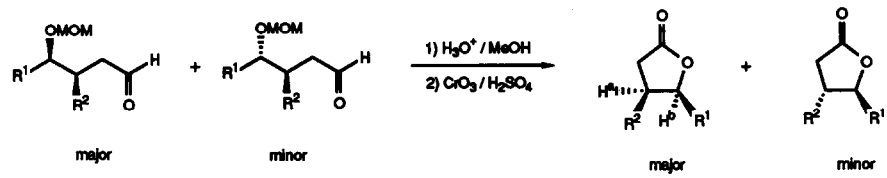
R^1	R^2	Yield, %[a] 1,4	1,2	Diastereoselectivity[b] optimum[c]	range[d]	1,4 - product average[e]
i-Pr	n-Bu	37	24	248:1	88 ->99	96 (4)
i-Pr	n-Pent	44	27	139:1	86 ->99	91 (4)
i-Pr	Ph	46	12	99:1	77 - 99	89 (6)
n-Bu	n-Bu	30	17	> 250:1	79 ->99	87 (5)
n-Bu	Ph	26	8	45:1	74 - 98	85 (5)

[a] Yield of chromatographed material.
[b] Determined by capillary GC analysis of crude reaction mixtures.
[c] Best diastereoselectivity observed, syn : anti.
[d] Range of selectivity observed as percent syn isomer.
[e] Average selectivity as percent syn isomer (number of trials).

was realized in more than one experimental trial. In contrast to the high diastereoselectivity observed for the 1,4-adducts, the 1,2-adducts were obtained as a mixture of diastereomers ranging from 50:50 to 60:40.

The relative stereochemistry of the 1,4 adduct major isomer could not be unambiguously assigned by ^{1}H-NMR. To determine the stereochemistry, 4 was derivatized to the 3,4-disubstituted butyrolactone 6 by acid

catalyzed hydrolysis of the MOM protecting group followed by Jones oxidation of the crude hydroxy-aldehyde. The major isomer was isolated as a crystalline solid which revealed a cis relationship of the 3,4-substituents upon x-ray crystal structure analysis. The ^{1}H-NMR coupling constant for Hab (see figure, Table II) was 5.49 Hz in the major (cis) isomer, and 7.73 Hz in the minor (trans) isomer. The stereochemistry of each butyrolactone prepared was assigned by comparison of the ^{1}H-NMR coupling constants of Hab for the major and minor isomers; see Table II. In each case, the major (cis) isomer exhibited a smaller coupling constant than the minor (trans) isomer, consistent with the data obtained for 6 whose stereochemistry was unambiguously defined by x-ray crystal structure. Since the cis-3,4-disubstituted butyrolactone results from the syn homoaldol product, the stereochemistry of the major isomer of the conjugate addition reaction can therefore be assigned as syn (Table I).



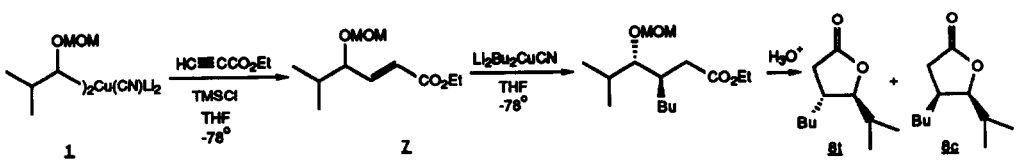
6 R^1 = i-Pr, R^2 = Ph

Table II Butyrolactone Synthesis and Spectral Data

R^1	R^2	Overall yield, %[a]	J Hab (Hz)[b] major isomer	J Hab (Hz)[b] minor isomer
i-Pr	Ph	36%	5.49	7.73
i-Pr	n-Bu	32%	4.96	5.08
i-Pr	n-Pent	24%	4.90	5.29
n-Bu	Ph	34%	6.48	
n-Bu	n-Bu	18%	6.18	6.80

[a] Overall yield of chromatographed butyrolactone product from the enal.
[b] Coupling constants in Hz for Hab, see 6.

As further proof of the stereochemical assignment, a selective trans-3,4-disubstituted butyrolactone synthesis was designed. Addition of the α-alkoxyorganocuprate 1 to ethyl propiolate, in the presence of in-situ TMSCl, resulted in the γ-alkoxy substituted enoate 7. Anti selective[9] addition of lithium dibutylcyanocuprate resulted in butyrolactone 8 upon aqueous acid hydrolysis of the MOM acetal.



The trans isomer 8t predominated (1:8.2, cis to trans) and was identical in all respects to the minor isomer (GC,TLC,NMR) isolated from the syn selective homoaldol methodology described earlier.

In summary, the conjugate addition of α-alkoxyorganocuprate reagents provides a highly selective route to syn homoaldol products. The syn homoaldol products are readily converted to cis-3,4-disubstituted butyrolactones in moderate overall yields with nearly complete stereoselectivity. In addition, a unique method for the enhancement of regioselectivity for organocuprate additions to enals has been disclosed[10].

Acknowledgments We would like to thank the donors of the Petroleum Research Fund, administered by the ACS, for support of this research, and Dr. Phirtu Singh for the x-ray crystal structure analysis.

References and Footnotes

1. Werstiuck, N. H. Tetrahedron, (1983), 39, 205; Hoppe, D. Angew. Chem. Int. Ed. Engl., (1984), 23, 932.
2. Hoppe, D.; Kramer, T. Angew. Chem. Int. Ed. Engl., (1986), 25, 160; (b) Nakamura, E.; Sekiya, K.; Kuwajima, I. Tetrahedron Lett., (1987), 28, 337; (c) Kramer, T.; Hoppe, D. Tetrahedron Lett., (1987), 28, 5149.
3. Heathcock, C.H. in "Asymmetric Synthesis", Morrison, J. D. Ed., Volume 3, pp. 111-212, Academic Press, New York, 1984.
4. Hoppe, D.; Hanko, R.; Bronneke. A.; Lichtenberg, F. Angew. Chem. Int. Ed. Engl., (1981) 20, 1024.
5. (a) Hoppe, D.; Gonschorrek, C.; Schmidt, D.; Egert, E. Tetrahedron (1987), 43, 2457; (b)Hoppe, D.; Lichtenberg, F. Angew. Chem. Int. Ed. Engl., (1984) 23, 239.
6. Linderman, R. J.; Godfrey, A.; Horne, K. Tetrahedron Lett., (1987), 28, 3911. For a non-regiospecific alternate approach see Chenard, B. L. Tetrahedron Lett., (1986), 27, 2805.
7. (a) Corey, E. J.; Boaz, N. W. Tetrahedron Lett., (1985), 26, 6019; (b) Alexakis, A.; Berlan, J.; Besace, Y. Tetrahedron Lett., (1986), 27, 1047; (c) Horiguchi, Y.; Matsujswa, S.; Nakamura, E.; Kuwajima I. Tetrahedron Lett., (1986), 27, 4025, 4029 : (d) Johnson, C. R.; Marren, T. J. Tetrahedron Lett., (1987), 28, 27.
8. (a) Chuit, C.; Foulon, J. P.; Normant, J. F. Tetrahedron, (1981), 37, 1385; (b) Clive, D. L. J.; Farina, V.; Beaulieu, P. L. J. Org. Chem., (1982), 47, 2572.
9. For examples of anti selective organocuprate addition to γ-substituted enoates see, Yamamoto, Y.; Nishii, S.; Ibuka, T. J. C. S., Chem. Commun., (1987), 464, and references therein.
10. A full account of this procedure using other α-substituted organocuprates will appear elsewhere. The improved regioselectivity is not limited to α-alkoxyorganocuprates.

(Received in USA 26 April 1988)