Tetrahedron Letters,Vol.27,No.38,pp 4553-4556,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

THE SYNTHESIS AND STEREOSELECTIVE CONJUGATE ADDITION REACTIONS OF α-ALKOXYORGANOCUPRATE REAGENTS

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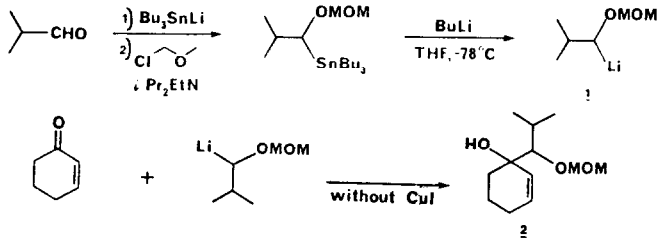
Abstract: α-Alkoxyorganocuprate reagents have been prepared from α-alkoxyorganostannanes. The cuprates undergo diastereoselective conjugate addition reactions with cyclohexenone with up to 8:92 selectivity. The effects of trimethylsilyl chloride on the chemical yields and the diastereoselectivity of the reaction are described.

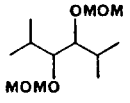
The preparation of α-alkoxyanions from α-alkoxyorganostannanes has been demonstrated by Still.[1] These configurationally fixed anions undergo alkylation reactions with complete retention of configuration.[1b] McGarvey and MacDonald[2] have studied the transmetallation of several α-alkoxystannanes and determined the relative order of stability for the derived anions. McCarvey[3] has subsequently illustrated additional synthetic utility of the anions in condensation reactions. There have been reports of α-alkoxycuprate reagents for unsubstituted (1°) alcohols[4]; however, there have been no reports of cuprate reagents generated from more highly substituted alcohols. We have initiated a study of the synthetic utility of α-alkoxyorganocuprates, and an investigation of the diastereoselectivity of these configurationally fixed (sp^3) cuprates in conjugate addition reactions.

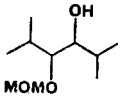
Conjugate addition reaction of cuprates to γ-substituted enones in both cyclic and acyclic cases occurs with a high degree of stereoselectivity anti to the γ-substituent.[5] Surprisingly little is known about the facial selectivity of a conjugate addition reaction in which the selectivity is due to the transferred ligand from the cuprate complex. Configurationally stable cuprate reagents have been prepared and were shown to undergo nucleophilic displacement[6] and conjugate addition reactions[7] with retention of configuration at the anionic center. The conjugate addition reaction in this example did not produce a new chiral center. Morgans[8] has reported an example of a stereoselective conjugate addition reaction with a cyclopropyl cuprate species resulting in 5.6:1 selectivity at the enone β-carbon. It is reasonable to assume, based on steric arguments, that an sp^3 cuprate would provide an even greater degree of selectivity.

α-Alkoxystannane 1 was prepared by the method by Still.[1a] Transmetallation with nBuLi in THF at -78°C and addition of the lithio anion to a solution of cyclohexenone produced the unstable 1,2-addition product 2. GC analysis of the crude product mixture indicated that no 1,4-addition had occurred. Conditions for the reproducible formation of the cuprate were then developed. The cuprate reagent formed quite readily, as noted by the absence of 2 in the reaction with cyclohexenone; however, the yields of 1,4-addition

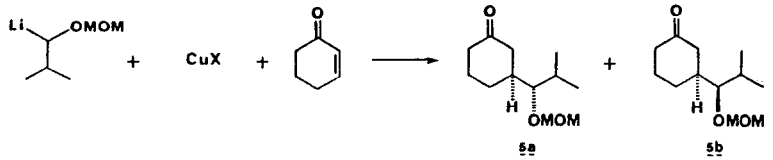


product were initially very low. Two by-products were noted by GC analysis of the crude reaction mixture. After isolation, the dimeric species 3 and the alcohol 4 were identified by ^{1}H-NMR, GC/MS and ultimately by independent synthesis.[9] The alcohol 4 can be detected in THF solutions of the α-alkoxylithio species (without CuI) within 30 minutes at -78°C. We determined that formation of these by-products would be reduced if extreme care was taken in the purification of the α-alkoxystannanes.





The yield of the conjugate addition product 5 was substantially improved by carrying out the reaction in the presence of trimethylsilylchloride (TMSCl), see Table I. Corey[10a] and Alexakis[10b] have reported a pronounced rate enhancement and considerable improvement in the yields of conjugate addition reactions using this procedure. From Table I it is also apparent that the yield of the reaction is also dependent on the cuprate formation and the reaction times. Longer formation times lead to decreased yields of 5, presumably due to decomposition of the cuprate. A synthetically useful yield (95%) was obtained by using either the homo- or higher order cuprate reagent, Table I entries 11 and 12.



The facial selectivity of the reaction was determined by capillary GC analysis.[11] Although the isomer ratio could also be determined by integration of the ^{1}H-NMR spectra of 5, the assignment of the stereochemistry of the major isomer was not possible. The

cyano cuprate reagent, in the presence of TMSCl, gave a reproducible ratio of 20:80. A slight decrease in selectivity was noted for both the homo- and higher order cuprates. This observation prompted the comparison of the facial selectivity in the absence of TMSCl, see Table II. The cyano and higher order cuprates exhibited greater stereoselectivity without TMSCl present, but the chemical yields were reduced.

Corey[12] has provided chemical evidence that conjugate addition reactions proceed by initial d-π^* complexation with subsequent formation of a β-Cu (III) intermediate, and that these steps are reversible. The addition of TMSCl presumably causes an irreversible reaction leading to increased yields of conjugate addition product by reducing competing enolate reactions.[10] The decrease in the facial selectivity observed for the cyano and higher order cuprate reagents may be due to the rate enhancement effect of TMSCl; however, this explanation does not hold for the hexynyl or homocuprate reagents. The selectivity for these reactions was virtually unchanged with or without TMSCl. The non-transferable ligand must therefore play some role in the diastereoselectivity of the conjugate addition reaction of α-alkoxy-organocuprate reagents. We are currently investigating the phenomenon with other non-transferable ligands on copper, and attempting to prepare separable derivatives of 5 for the unambiguous assignment of the stereochemistry. The synthetic utility of these novel functionalized organocuprate reagents derived from other aldehydes will be reported in due course.

Acknowledgements: We would like to thank Research Corporation-Cottrell Research Grant and NCSU Biomedical Research Support Grant No. RR7071 for financial support.

References and Footnotes:

1. (a) W.C. Still, J. Amer. Chem. Soc., 100, 1481 (1978), (b) W.C. Still and C. Sreekumar, J. Amer. Chem. Soc., 102, 1201 (1980).
2. J.S. Sawyer, T.L. MacDonald, and G.J. McGarvey, J. Amer. Chem. Soc., 106, 3376 (1984).
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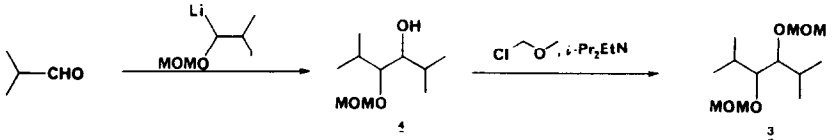
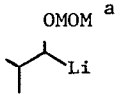
4. (a) E.J. Corey and T.M. Eckrich, Tetrahedron Lett., 24, 3165 (1983); (b) R.K. Boeckman and S.H. Choen, J. Amer. Chem. Soc., 105, 4112 (1983).
5. see inter alia S. Hanessian, P.J. Murray, and S.P. Sahoo, Tetrahedron Lett., 26, 5627 (1985); W.R. Roush and B.M. Lesur, Tetrahedron Lett., 24, 2231 (1983).
6. C.R. Johnson and G.A. Dutra, J. Amer. Chem. Soc., 37, 7777 (1973).
7. G.M. Whitesides and P.E. Kendall, J. Org. Chem., 37, 3718 (1972).
8. D.J. Morgens and G.B. Feigelson, J. Amer. Chem. Soc., 105, 5477 (1983).
9. The compounds 3 and 4 were prepared by the following sequence:



4 3

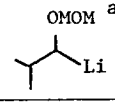
10. (a) E.J. Corey and N.W. Boaz, Tetrahedron Lett., 26, 6019 (1985); (b) A. Alexakis, J. Berlan and Y. Besace, Tetrahedron Lett., 27, 1047 (1986).
11. The diastereoisomers were separable on a SE 30, 25m column using a temperature program of 100°/10 min., 100°-250° at 10/min.
12. E.J. Corey and N.W. Boaz, Tetrahedron Lett., 26, 6015 (1985).

Table I Conjugate Addition Reactions in the Presence of Trimethylsilyl Chloride

Entry	CuX	 [a]	Formation[b] time, hrs.	Reaction[c] time, hrs.	Yield[d] %,5	Selectivity[e]
1	CN	1	1	1	43	21:79
2	CN	1	1	3	50	18:82
3	CN	1	1	5	53	18:82
4	CN	1	3	1	34	20:80
5	CN	1	3	3	30	21:79
6	CN	1	3	5	55	19:81
7	CN	1	5	1	37	21:79
8	CN	1	5	3	27	20:80
9	CN	1	5	5	35	21:79
10	Hexynyl	1	1	5	46	28:72
11	I	2	1	5	94	25:75
12	CN	2	1	5	96	30:70

[a]Equivalents to CuX; [b]The lithio anion was added to a suspension of CuX in THF at -78°C and allowed to warm to -35°C over 1 hr and maintained at -35°C if formation periods longer than 1 hr were used; [c]Cyclohexenone (1 equiv.) and TMSCl (5 equiv.) were combined in THF at -78°C and then transferred via cannula to the cuprate reagent at -78°C; [d]Yield of chromatographed material 5: Anal Calc; C; 67.26; H: 10.35; Found C: 67.20; H: 10.38; [e]Diasteromeric ratio determined by cap. GC and verified by GC/MS, each peak exhibited identical mass spectra.

Table II Conjugate Addition Reactions in the Absence of Trimethylsilyl Chloride

Entry	CuX	 [a]	Formation[b] time, hrs.	Reaction[c] time, hrs.	Yield[d] %,5	Selectivity[e]
1	CN	1	3	3	20	8:92
2	CN	2	1	5	35	9:91
3	Hexynyl	1	3	3	20	25:75
4	I	2	1	5	22	27:73

[a-e]see legend Table I.

(Received in USA 17 June 1986)