Tetrahedron Letters, Vol. 34, No. 38, pp. 6037-6040, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Diastereoselective 1,6-Addition Reactions of Organocuprates to Chiral 5-Alkynylidene-1,3-dioxan-4-ones

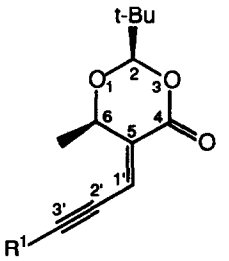
Gabriele Handke and Norbert Krause*

Institut für Organische Chemie der Technischen Hochschule Darmstadt,
Petersenstraße 22, D-64287 Darmstadt, Germany

Abstract: 1,6-Addition reactions of organocuprates to 5-alkynylidene-1,3-dioxan-4-ones **1-4** and regioselective protonation with pivalic acid furnished allenic dioxanones **5-12** with diastereoselectivities of up to 94:6. Adduct **5a/b** (ds = 80:20) was converted into chiral non-racemic vinylallene **13** (60% ee).

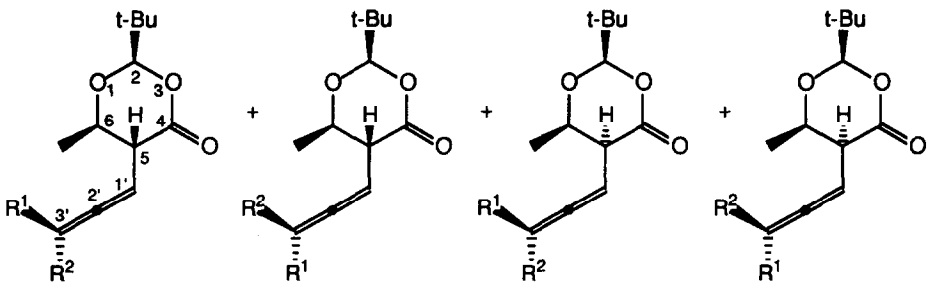
In modern Organic Chemistry a large number of methods is available for the stereoselective synthesis of molecules bearing centers of chirality. In contrast to this, the number of schemes for the preparation of compounds with axial chirality, e.g. allenes, is rather limited. Chiral, non-racemic allenes are usually synthesized by [2,3] sigmatropic rearrangements of derivatives of chiral propargylic alcohols[1,2]; however, due to the often difficult accessibility of the latter, this method is not generally applicable. In connection with our studies on the 1,6-addition of organocuprates to acceptor-substituted enynes and trapping reactions of the allenyl enolates thus formed[3], we sought to use this new method to open an access to functionalized chiral, non-racemic allenes.

Since our attempts to employ enantioselective 1,6-addition reactions of cuprates RCu(L*)Li bearing chiral ligands L*[4] to 2-en-4-ynoates failed[5], we concentrated our efforts on diastereoselective 1,6-additions of achiral homo- or cyanocuprates to chiral acceptor-substituted enynes. In these experiments, acyclic enynes with chiral substituents at different positions of the molecule gave only unsatisfactory diastereoselectivities of up to 2:1[5]; thus, it seems to be necessary to limit the degrees of freedom by using cyclic Michael acceptors. This finding and reports of highly diastereoselective 1,4-addition reactions of cuprates to chiral 5-alkylidene-1,3-dioxan-4-ones[6] prompted us to examine diastereoselective 1,6-addition reactions of cuprates to 5-alkynylidene-6-methyl-2-(1,1-dimethylethyl)-1,3-dioxan-4-ones **1-4** which were obtained from 6-methyl-2-(1,1-dimethylethyl)-1,3-dioxan-4-one[5,7]. The 1,6-addition of lithium dimethylcuprate ($Me_2CuLi \cdot LiI$) or lithium di-t-butylcyanocuprate ($t\text{-}Bu_2Cu(CN)Li_2$) to **1-4** and regioselective protonation with pivalic acid[3a,c] furnished allenic dioxanones **5-12** (see Table)[5].



1 - 4

1. $Me_2CuLi \cdot LiI$ or
   $t\text{-}Bu_2Cu(CN)Li_2$, Et_2O, -20°C
2. $t\text{-}BuCO_2H$, Et_2O, -80°C



a **b** **c** **d**

5 - 12

Enyne	R^1	R^2	Allene	**a** : **b** : **c** : **d** [a]	Yield (%)
1	t-Bu	Me	**5**	67 : 17 : 8 : 8	78
1	t-Bu	t-Bu	**6**	> 98 : < 2	68
2	Me_3Si	Me	**7**	69 : 17 : 7 : 7	47
2	Me_3Si	t-Bu	**8**	94 : 6 : 0 : 0	47
3[b]	n-Bu	Me	**9**	28 : 52 : 15 : 5	36
3[b]	n-Bu	t-Bu	**10**	46 : 54 : 0 : 0[c]	56
4	H	Me	**11**	45 : 55 : traces	53
4	H	t-Bu	**12**	63 : 37 : traces	30

a) Determined by integration of the signals for 2-H in the ^1H NMR spectra of the crude products.

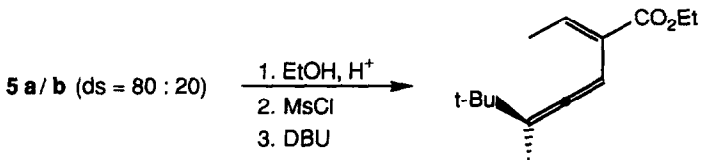
b) Racemate.

c) Protonation with 2N sulfuric acid.

The diastereoselectivities of the 1,6-addition and of the protonation depend on the steric properties of the enyne and the cuprate. Thus, reaction of **1** with $Me_2CuLi \cdot LiI$ and pivalic acid provided allene **5** as a 67:17:8:8 mixture of diastereomers; after chromatography, a mixture of the major isomers **5a/b**[8] (ds = 80:20) was obtained. The coupling constant $J_{5,6}$ = 9.7 Hz shows that both diastereomers possess a trans configuration at the dioxanone ring. By determination of the X-ray structure of the analogous adduct bearing a methyl group at C-5 (obtained from **1** with $Me_2CuLi \cdot LiI$ and MeOTf; ds = 70:30; 75% yield[5]) and comparison of the NMR data it could be established that the major diastereomer of **5** has a (2R,5R,6R,2'S) configuration (structure **5a**), i.e. the attack of the cuprate is controlled by the methyl group at C-6 of the dioxanone ring and takes place preferably from the less hindered bottom side. Reaction of **1** with $t\text{-}Bu_2Cu(CN)Li_2$ and pivalic acid furnished adduct **6a** as only product, i.e. in this case the protonation occurs with complete regio- and stereoselectivity. Similarly, the trimethylsilyl-substituted enyne **2** reacted with lithium dimethylcuprate to give allene **7** as a 69:17:7:7 mixture of isomers; with lithium di-t-butylcyanocuprate, a high degree of diastereoselection (94:6) could be reached.

In contrast to this, 1,6-addition reactions of cuprates to enynes **3** and **4** bearing an n-butyl group or a hydrogen atom at C-3' proceeded less selectively, furnishing adducts **9-12** (see Table). Interestingly, the NMR data seem to indicate that for allenes **9-11** isomer **b** is the major product, i.e. attack of the cuprate from the upper side of the dioxanone ring is prevailing. Another surprising finding was made when the protonating agent was changed: it was found that *the configuration of the allene moiety is not established in the 1,6-addition reaction, but is also dependent on the protonating agent.* Thus, reaction of enyne **1** with $Me_2CuLi \cdot LiI$ and 2N sulfuric acid furnished allene **5a/b** as a 44:56 mixture of diastereomers; protonation with water gave a ratio of 31:69[5]! This shift in diastereoselectivity is not caused by an isomerization taking place after workup; treatment of an 80:20 mixture of **5a/b** with 2N sulfuric acid did not induce a change of this ratio (at longer reaction times the acetal moiety is cleaved)[5]. A mechanistic rationalization for these observations has to await investigations of the structure of allenyl enolates.

Allenic dioxanones of type **5-12** can serve as precursors for chiral, non-racemic vinylallenes which are of interest as dienes for Diels-Alder reactions[1]. For example, acid catalyzed hydrolysis of **5a/b** (ds = 80:20) and esterification provided the corresponding allenic β-hydroxyester; this was converted into acceptor-substituted vinylallene **13** by mesylation and mesylate elimination with DBU (the latter takes place stereoselectively as syn-elimination to give the E-isomer exclusively). Vinylallene **13**[9] was obtained with 45% overall yield and 60% ee, i.e. the stereochemical information of the allene moiety gained in the 1,6-addition reaction is preserved in this conversion. Further work concerning the mechanism and synthetic applications of diastereoselective 1,6-addition reactions is in progress.



1 3

60% ee (45% Yield)

Acknowledgement. Support of this work by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the Chemetall GmbH (Frankfurt) is gratefully acknowledged.

References and Notes

[1] a) S. Patai (Ed.), *The Chemistry of Ketenes, Allenes and Related Compounds,* Wiley, New York, **1980**.
b) S.R. Landor (Ed.), *The Chemistry of the Allenes,* Academic Press, London, **1982**.
c) H.F. Schuster, G.M. Coppola, *Allenes in Organic Synthesis,* Wiley, New York, **1984**.

[2] a) N. Krause, G. Handke, *Tetrahedron Lett.* **1991**, *32,* 7225-7228, and literature cited therein.
b) S. Dreller, M. Dyrbusch, D. Hoppe, *Synlett* **1991**, 397-400.
c) A. Alexakis, *Pure Appl. Chem.* **1992**, *64,* 387-392.
d) S.K. Kang, S.G. Kim, D.G. Cho, *Tetrahedron: Asymmetry* **1992**, *3,* 1509-1510.
e) T. Konoike, Y. Araki, *Tetrahedron Lett.* **1992**, *33,* 5093-5096.

[3] a) N. Krause, *Chem. Ber.* **1990**, *123,* 2173-2180.
b) N. Krause, *Chem. Ber.* **1991**, *124,* 2633-2635.
c) S. Arndt, G. Handke, N. Krause, *Chem. Ber.* **1993**, *126,* 253-259.
d) N. Krause, S. Arndt, *Chem. Ber.* **1993**, *126,* 261-263.

[4] a) B.E. Rossiter, N.M. Swingle, *Chem. Revs.* **1992**, *92,* 771-806.
b) N. Krause, *Kontakte (Darmstadt)* **1993** (1), 3-13.

[5] G. Handke, Ph.D. Thesis, TH Darmstadt, **1993**.

[6] a) W. Amberg, D. Seebach, *Chem. Ber.* **1990**, *123,* 2413-2428.
b) W. Amberg, D. Seebach, *Chem. Ber.* **1990**, *123,* 2429-2438.
c) W. Amberg, D. Seebach, *Chem. Ber.* **1990**, *123,* 2439-2444.

[7] a) D. Seebach, M. Züger, *Helv. Chim. Acta.* **1982**, *65,* 495-503.
b) D. Seebach, A.K. Beck, R. Breitschuh, K. Job, *Org. Synth.* **1992**, *71,* 39-47.
c) H.-M. Müller, D. Seebach, *Angew. Chem.* **1993**, *105,* 483-509; *Angew. Chem. Int. Ed. Engl.* **1993**,*32,* 477-502.

[8] **5a/b** (80:20): colorless crystals, m.p. 67-68°C. ^{1}H NMR (*: major isomer): δ = 0.97 (s, 9H, 2-$(CH_3)_3$), 1.05/1.07* (2s, 9H, 3'-$C(CH_3)_3$), 1.36/1.37* (2d, 3H, 2xJ = 6.1 Hz, 6-CH_3), 1.71*/1.72 (2d, 3H, 2xJ = 2.9 Hz, 3'-CH_3), 2.91*/2.91 (2dd, 1H, J = 6.9/9.7 Hz **[5a]** / 6.3/9.7 Hz **[5b]**, 5-H), 3.83*/3.86 (2 dq, 1H, 2xJ = 9.7/6.1 Hz, 6-H), 4.91/4.92* (2s, 1H, 2-H), 5.22*/5.34 (2dq, 1H, J = 6.9/2.9 Hz **[5a]** / 6.3/2.9 Hz **[5b]**, 1'-H).

[9] **13**: colorless oil; $[\alpha]_D$ = -33.0 (c = 1.04, EtOH), 60% ee (by ^{1}H NMR spectroscpoy with $Eu(hfc)_3$). ^{1}H NMR: δ = 1.05 (s, 9H, $C(CH_3)_3$), 1.29 (t, 3H, J = 7.1 Hz, $OCH_2\underline{CH_3}$), 1.74 (d, 3H, J = 3.0 Hz, 5-CH_3), 1.88 (d, 3H, J = 7.3 Hz, 2'-H), 4.20 (q, 2H, J = 7.1 Hz, OCH_2), 6.04 (q, 1H, J = 3.0 Hz, 3-H), 6.79 (q, 1H, J = 7.3 Hz, 1'-H).

(Received in Germany 19 May 1993; accepted 22 July 1993)