Tetrahedron Letters,Vol.30,No.16,pp 2079-2082,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

# ENANTIOSELECTIVE SYNTHESIS OF SILOXYCYCLOPROPANES AND OF γ-OXOCARBOXYLATES BY ASYMMETRIC CATALYSIS

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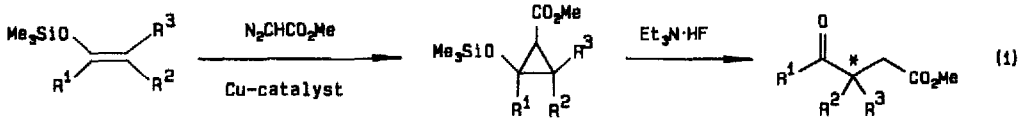
Summary: Up to 48% enantiomeric excess have been attained by cyclopropanation of silyl enol ethers with methyl diazoacetate in the presence of optically active Cu-catalysts. Subsequent ring opening of resulting siloxycyclopropanes gives γ-oxocarboxylates with a maximum enantiomeric excess of 37%.

Asymmetric catalysis allows enzyme-like amplification of chirality, and several highly impressive examples are already known[2]. Enantioselective synthesis of cyclopropane derivatives[3-7] with the aid of optically active catalysts and diazo compounds is one of relatively few C-C bond forming reactions which provide high enantiomeric excess (ee) in certain cases. However, rather simple olefins have usually been employed, and to our knowledge only one case is reported[8] where preparation is joined by a suited ring opening reaction of the cyclopropane. We want to disclose our preliminary results on the enantioselective cyclopropanation from silyl enol ethers **1** to siloxycyclopropanes **2** which can be converted to optically active γ-oxocarboxylates **3** under very mild conditions (equation 1)[9]. The latter are very versatile intermediates for further synthetic transformations, as demonstrated for the racemic compounds[10].

Results: We started with literature known catalysts like the Schiff-base Cu(II) complex **4a**[4,5], or the $C_2$-symmetrical "semicorrin" complex **5** developed by Pfaltz[7]. The ligands in **4** and **5** are elaborated from natural L-amino acids. Although the γ-oxocarboxylates **3a** and **3b** attainable from cyclopropanes **2a** and **2b** are not chiral, the silyl enol ethers **1a** and **1b** have been included in this study. The enantioselectivities are compared to those obtained with olefins as styrene. As disclosed in the table (entries 1-3) the cyclopropanations of these siloxyalkenes occur with moderate enantioselectivity. With the Pfaltz catalyst **5**, 48% ee have been determined[11] for the trans-diastereomer of **2b**. The predominating absolute configurations (at C-1) could not be established. Nevertheless, it is interesting to note that the sense of optical rotation in the diastereomeric mixtures of **2a** and **2b** is subject to the choice between Schiff-base catalysts **4** or the "semicorrin" complex **5**. This suggests opposite induction by these catalysts, as has been proven for silyl enol ethers **1c** - **1e** (entries 4-10).

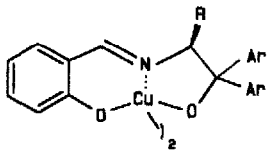
Cyclopropanation of silyl enol ether **1c** has been investigated in much detail because of the particular synthetic potential of ring cleavage product **3c**. Standard Schiff-base complex **4a** - derived from L-phenylalanine - gave an enantiomeric excess of 41% for the major trans-diastereomer, whereas the cis-cyclopropane is formed as a racemic mixture (entry 4). Ring

opening affords the γ-oxocarboxylate **3c** in 29% ee. Its predominating R-configuration at C-3 could be established by comparison with literature data [12]. This also allows to define the configuration of C-1 in trans-2c to be mainly R. With optically active **3c** it was proven, that $NEt_3 \cdot HF$ does not induce racemization at the chiral centre under the reaction conditions employed for ring cleavage.



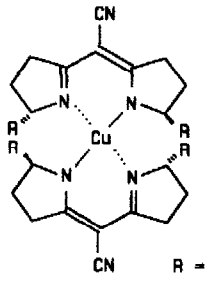

1 2 3

**a** $R^1$, $R^2$, $R^3$ = H
**b** $R^1$ = Ph, $R^2$, $R^3$ = H
**c** $R^1$, $R^2$ = H, $R^3$ = Me
**d** $R^1$, $R^2$ = H, $R^3$ = i-Prop
**e** $R^1$-$R^2$ = $-(CH_2)_3-$, $R^3$ = H




4

**a** R = $CH_2Ph$, Ar = Ph
**b** R = t-Bu, Ar = Ph
**c** R = $CH_2Ph$, Ar = o-Me-$C_6H_4$-




R = $-C(CH_3)_2OH$

5

Use of the new catalyst **4b** - prepared from L-tert-butylleucine[1] - did not improve the enantioselectivity (entry 5). On the contrary, the overall chirality transfer to 3 is only 5%. However, replacing the two phenyl groups of **4a** by o-methoxy phenyl substituents to give catalyst **4c** raises the ee to 25% for cis-2c and to 46% for the major isomer trans-2c (entry 6). Thus, γ-oxocarboxylate **3c** is obtained with 37% ee and predominant R-configuration at C-3. This value allows determination of the dominating absolute configurations for both cyclopropane isomers as indicated in the table[13]. Pfaltz catalyst 5 gives very similar figures (entry 7), with the exception that the trans:cis ratio is significantly higher and the absolute stereochemistry is inverted.

The behaviour of the isopropyl substituted silyl enol ether 1d is rather puzzling (entry 8): first, the low trans:cis ratio is surprising, second, the cis-isomer 2d shows the higher enantiomeric excess with 40% as compared to only 2% for trans-2d. For 3d, preference of C-3 with R-configuration could be established[14]. Cyclic silyl enol ether 1e gives comparable results with catalysts **4a** and 5 (entries 9 and 10), but with opposite absolute stereochemical inductions. The values are comparable to those obtained for 1c, however, the overall ee in 3e is much lower since the trans:cis ratio is almost 1:1. Ketoester 3e is also known in optically active form[15] thus allowing assignments of the absolute stereochemistry as indicated in the table.

Table: Synthesis of Siloxycyclopropanes 2 and of γ-Oxocarboxylates 3 by Enantioselective Cyclopropanation of Silylenolethers 1 (in $C_6H_6$) and Subsequent Ring Cleavage with $Et_3N \cdot HF$.

| Entry | Sily Enol Ether 1 | Catalyst[a] [Equiv.] | Temp.[b] [°C] | Cyclopropane [cis:trans] | Yield [%] | Enantiomeric Excess [%][c] cis-2 | trans-2 | γ-Oxocarboxylate 3 Yield [%] | ee [%][d] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1a | 4a (2.0) | 80 | 2a 28:72 | 53 | 30 (-)[e] | 30 | - | |
| 2 | 1a | 5 (1.0) | 80 | 2a 25:72 | 43 | 12 (+) | 33 | - | |
| 3 | 1b | 5 (1.6) | 80 | 2b 45:55 | 53 | 40 (+) | 48 | - | |
| 4 | 1c | 4a (2.0) | 50 | 2c 22:78 | 62 | 0 | 41 (R) | 3c 73 | 29 (R) |
| 5 | 1c | 4b (2.0) | 50 | 2c 27:73 | 56 | - | - | 3c 87 | 5 (R) |
| 6 | 1c | 4c (2.0) | 50 | 2c 25:75 | 48 | 25 (S) | 46 (R) | 3c 74 | 37 (R) |
| 7 | 1c | 5 (2.0) | 70 | 2c 15:85 | 40 | 15 (R) | 40 (S) | 3c 76 | 37 (S) |
| 8 | 1d | 4a (2.0) | 50 | 2d 44:56 | 60 | 40 (R) | 2 (?) | 3d 79 | 14 (R) |
| 9 | 1e | 4a (1.3) | 60 | 2e 55:45 | 71 | 15 (S) | 40 (S) | 3e 77 | 10 (R) |
| 10 | 1e | 5 (1.3) | 80 | 2e 48:52 | 54 | 15 (R) | 43 (R) | 3e 85 | 17 (S) |

[a] Catalysts 4 are generated *in situ* from $Cu(OAc)_2$ and the free ligand[5]. - [b] Temperatures are chosen as low as possible for maintaining nitrogen evolution. - [c] In parentheses: predominating absolute configuration at C-1. - [d] In parentheses: predominating absolute configuration at C-3. - [e] Sense of optical rotation of the diastereomeric mixture.

Conclusion: The data assembled in the table do not permit a unifying mechanistic interpretation. The crucial questions are addressed to the structure of the ***reactive conformation*** of the Cu(I)-carbene complex which is assumed to be involved[3], and to the ***approach of the olefins*** onto this carbenoid. In summary our experiments show the following features:

* Catalysts 4 cause opposite absolute configurations compared to semicorrin complex 5[7].

* Enlargement of the group R adjacent to the chiral carbon in 4 does not enhance the enantioselectivity, whereas variation of the aryl groups is more relevant[4].

* Of great importance is the observation that 4c causes the same absolute configuration at C-3 in both cyclopropane diastereomers 2c, since this is the only chiral centre being maintained after the ring cleavage to 3c. This holds also true for the Pfaltz catalyst 5.
  Usually these catalysts induce the same absolute stereochemistry at C-1 adjacent to the ester group if simple olefins as styrene are employed[4,5,7]. This difference demonstrates that the mechanistic schemes suggested for these cyclopropanations are not valid for additions to enol ethers[16].

The experiments presented in this study reveal trends which might be helpful for future design of more effective catalysts leading to enantioselectivities of practical value.

Acknowledgement: Generous support of this work by the Fonds der Chemischen Industrie, the Karl-Winnacker-Stiftung (Hoechst AG), and the Vereinigung von Freunden der Technischen Hochschule zu Darmstadt is gratefully appreciated. We are also very thankful to the Degussa AG for a gift of amino acids and in particular to Dr. A. Pfaltz (ETH Zürich) providing us with a sample of 5 and detailed experimental procedures for preparation of this semicorrin complex prior to publication.

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10) Review: H.-U. Reissig, Top. Curr. Chem. 144 (1988) 73.

11) The enantiomeric excess at the cyclopropane stage could be determined by 300 MHz $^1$H NMR spectroscopy using Eu(hfc)$_3$ as shift reagent in $CDCl_3$ or in $C_6D_6$.

12) Aldehyde 3c is known with 93% ee displaying an optical rotation $[\alpha]_D^{25}$ of -71.2°: A. Bernardi, S. Cardani, T. Pilati, G. Poli, C. Scolastico, R. Villa, J. Org. Chem. 53 (1988) 1600. The sample obtained from entry 6 has an $[\alpha]_D^{25}$ of -26.1°. The calculated ee of 37% is confirmed by application of shift reagent.

13) R-Configuration at C-3 for both cyclopropane diastereomers of 2c should give an ee of 40% for 3c [0.75·46% + 0.25·26% = 40%]. S-Configuration at C-3 in the minor diastereomer should give an ee of only 28% [0.75·46% - 0.25·26% = 28%]. The analog calculations led to the other assignments given in the table.

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15) J.J. Partridge, N.K. Chadha, M.R. Uskokovic, J. Am. Chem. Soc. 95 (1973) 7171.

16) Another dissimilarity observed is the fact that use of tert-butyl instead of methyl diazoacetate decreases the enantioselectivity (for 1c and catalyst 5 or 4)[1]. Usually, sterically more demanding ester substituents increase enantioselectivity remarkably[4,7].

(Received in Germany 27 January 1989)