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Diastereoselectivity in the 1,2-Addition of Silylazoles to Chiral Aldehydes. Stereocontrolled Homologation of α-Hydroxyaldehydes.

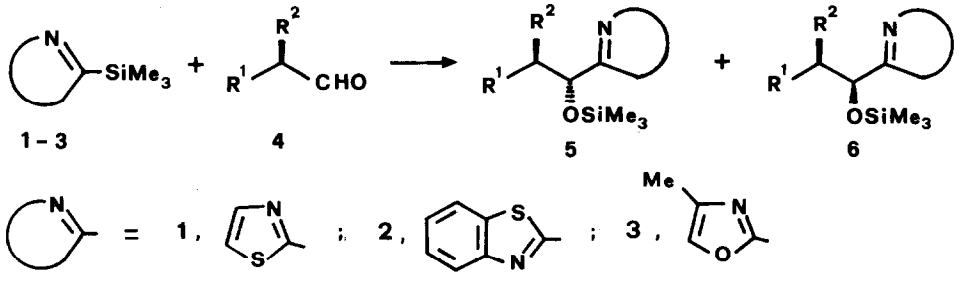
Alessandro Dondoni*, Marco Fogagnolo, Alessandro Medici, and Paola Pedrini

Dipartimento di Chimica, Università di Ferrara, Ferrara, Italy

The addition of 2-trimethylsilylazoles (thiazole, benzothiazole, oxazole) to α-asymmetric aldehydes give the corresponding O-silylcarbinols in good chemical yield and high stereoselectivity; the reaction is employed for the stereoselective homologation of D-glyceraldehyde.

Asymmetric control in carbon-carbon bond forming reactions is one of the major challenge in organic synthesis.[1] Various stereoselective additions of organometallics to carbonyl compounds have been reported,[2] but only in a few instances the organic nucleophile was an heterocyclic ring.[3] Yet, chiral building blocks bearing an heterocylic ring are particularly useful in view of further synthetic elaborations where the heterocycle can play the role of a masked functionality or a specific activator.[4] We here report on the significant stereoselectivity in the carbon-carbon bond formation between silylazoles and aldehydes.

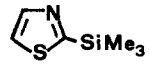
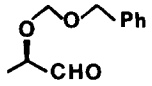
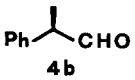
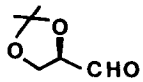
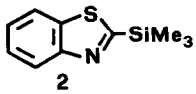
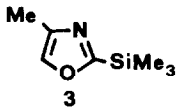
We have recently described the reaction of 2-trimethylsilylthiazole (**1**) with representative aromatic and aliphatic aldehydes to give the corresponding secondary O-trimethylsilylcarbinols in good yield.[5] Formally, this reaction corresponds to the 1,2-addition of the C-Si bond of (**1**) to the C=O of the aldehyde. Further to that, we have considered the possibility of exerting an asymmetric control on the reaction by using aldehydes bearing an α-chiral centre. Thus, the addition of (**1**) to α-asymmetric aldehydes (**4a-c**) (Scheme 1) proceeded under mild conditions in good chemical yield and



Scheme 1

significant stereoselectivity (Table).

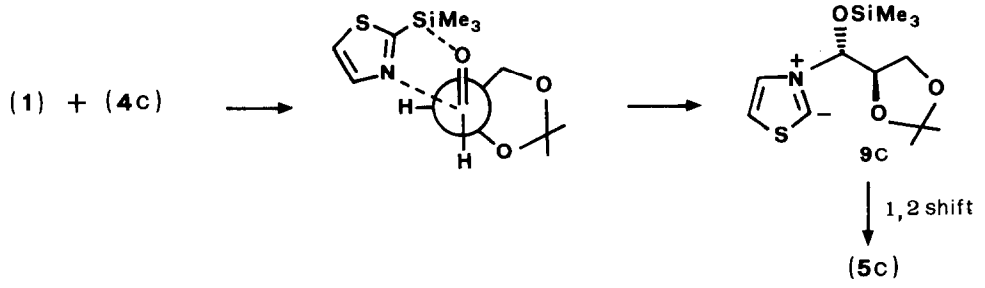
TABLE.

Run	Azole	Aldehyde	5,6	Products[a] Ratio 5:6 (yield %)	Solv./Temp. Time(h)	$\delta(CDCl_3)$[b] J_{HHvic} (Hz) 5	6
1	 **1**	 **4a**	**a**	33:66 (70)	CH_2Cl_2/rt 4	5.10 3.91[c]	4.85 4.80
2	**1**	 **4b**	**b**	73:27 (73)	neat/0°C 6	5.06 4.81[d]	5.05 6.82
3	**1**	 **4c**	**c**	>95:<5 (93)	CH_2Cl_2/rt 4	5.07 5.10[e]	4.92 6.01[f]
4	 **2**	**4c**	**d**	80:20 (65)	neat/rt 24	5.15 5.32	5.01 5.67
5	 **3**	**4c**	**e**	21:79 (60)	neat/rt 24	4.64 5.85[g]	4.70 6.06[g]

[a]Diastereomeric ratios (NMR) and yields (overall on isolated products) refer to the desilylated carbinols. [b]NMR data refer to the proton of the formed epimeric centre. [c]L. M. Jackman, S. Sternhell in "Application of Nuclear Magnetic Resonance Spectroscopic in Organic Chemistry", 2nd edn., vol. 5, Pergamon Press, Oxford, 1969, pag. 291. [d]C. A. Kingsbury, W. B. Thornton, J. Org. Chem., **31**, 1000 (1966). [e]D. Horton, J. B. Hughes, J. K. Thomson, J. Org. Chem., **33**, 728 (1968). [f]The NMR data of **6c** have determined on a sample obtained for 2-Lithiothiazole and **4c**. [g]Due to the very closed values of the two coupling costants, these assignements will be checked by further experiments.

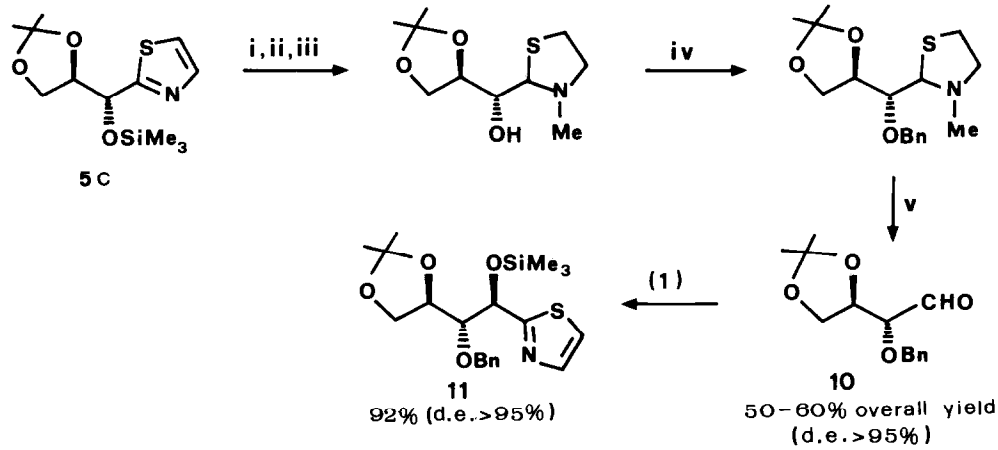
In particular the reaction of (**1**) with D-glyceraldehyde acetonide (**4c**) gave the anti-isomer (**5c**) with >95% diastereomeric purity.[6] A significant stereoselection was observed also in the addition of 2-trimethylsilylbenzothiazole (**2**) and 4-methyl-trimethylsilyloxazole (**3**)[7] to (**4c**). On the other hand, the reactions of 2-lithiothiazole and its benzo-derivative with the same aldehyde (**4c**) (Et_2O, -78°C) showed a complete lack of stereoselectivity (**5c**:**6c**, 50:50). Concerning the diastereoselectivity, this appeared to vary depending on the azole (runs 3-5) and the substituents at the chiral centre of the aldehyde (runs 1-3). Although further work is required to clarify the mechanistic origins of the observed effects, we now suggest that the exclusive anti-selectivity in the addition of the silylthiazole (**1**) to the aldehyde (**4c**) is compatible with a four-centre

transition state[8] (Scheme 2) where bonding between nitrogen of the thiazole ring and carbon of the carbonyl occurs in concert with transfer of the silyl group from C-2 to oxygen. This would lead to a 2-thiazolium ylide[9] (**9c**) which by 1,2-shift of the N-silyloxy moiety gives the final adduct (**5c**). As the stereochemical outcome of the reaction has been determined at the level of the ylide formation, the latter process must occur with retention of configuration.[10] The stereorandom addition of 2-lithiothiazole to (**4c**) indirectly supports the above hypothesis.



Scheme 2

For the equivalence of a C-2 substituted thiazole with an aldehyde,[11] the adduct (**5c**) can be considered a masked form of aldehydo-D-erythrose. Accordingly, unmasking the formyl group of (**5c**) (Scheme 3) using suitable reactions from the literature,[11] the trialkoxy derivative of D-erythrose (**10**) was obtained in 50-60% overall yield and >95% diastereomeric excess.[12] Therefore, the 1,2-addition between 2-trimethylsilylthiazole (**1**) and D-glyceraldehyde acetonide (**4c**) provides an high stereocontrolled homologation of the latter with good chemical yield. The reaction of (**1**) with (**10**) proved to be equally anti-diastereoselective (>95%) to give the adduct (**11**) in good yield.[13]



i, THF, H_2O/F^-; ii, SO_2, $Me_3O^+BF_4^-$; iii, EtOH, $NaBH_4$; iv, THF, NaH, $IN(Bu)_4$, BnBr; v, MeOH, H_2O, $HgCl_2$.

Scheme 3

Compound (**11**), which is a masked form of aldehydo-D-ribose is an attractive chiral building-block suitable for selective synthetic elaborations owing to the different protections of the hydroxyl groups. One can in principle repeat this reiterative sequence and prepare chiral anti-1,2-polyol systems. The rationale behind this project is the fact that the 1,2-diol moiety occurs in a moltitude of natural products such as pheromones, macrolides and all carbohydrates.

In conclusion, this preliminary work shows that the addition of 2-trimethylsilylthiazoles and oxazoles to chiral aldehydes can be a highly stereoselective and thus synthetically useful process.

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References and Notes

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5. A. Medici, G. Fantin, M. Fogagnolo, A. Dondoni, Tetrahedron Lett., **24**, 2901 (1983).
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7. A. Dondoni, T. Dall'Occo, G. Fantin, M. Fogagnolo, A. Medici, P. Pedrini, J.C.S. Chem. Commun., 258 (1984).
8. The aldehyde is oriented according to the Cram's open-chain model (Ref. 2a).
9. The mechanism via thiazolium ylide appears quite general for carbodesilylation of (**1**) and unlike that suggested in our previous report (Ref. 4), this should hold also for reactions with aldehydes. See also: A. Dondoni, Phosphorus and Sulphur and the Related Elements, **24**, 1 (1985).
10. This a formal Stevens rearrangement |S. H. Pine, Org. React., **18**, 403 (1970)| which is well known to occur with retention of configuration.
11. L. J. Altman, S. L. Richheimer, Tetrahedron Lett., 4709 (1971); A. I. Meyers, R. Munavu, J. Durandetta, ibid., 3929 (1972).
12. The compound (**10**) showed the following data: IR (film) 1745, 1460, 1380 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.65 (d, 1H, J = 2.1 Hz), 7.32 (s, 5H), 4.65 (d, 2H), 4.48-3.87 (m, 3H), 3.8 (dd, 1H, J = 2.1 Hz, J = 6.4 Hz), 1.42 (s, 3H), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 201.4 (d), 137.2 (s), 128.7 (d), 128.3 (d), 110.2 (s), 83.3 (dd), 75.2 (d), 73.5 (d), 66.3 (t), 26.5 (q), 25.2 (q); $|\alpha|_D$ +29.2 (c 2.747, $CHCl_3$).
13. The structure of compound (**11**) was established by X-ray crystallography: ^{1}H NMR ($CDCl_3$) δ 7.78 (d, 1H, J = 3.3 Hz), 7.34 (m, 6H), 5.22 (t, 1H, J = 4.4 Hz), 4.68 (d, 2H), 4.31-3.82 (m, 4H), 3.52 (d, 1H, J = 4.4 Hz), 1.38 (s, 3H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.2 (s), 142.3 (d), 138.1 (s), 128.6 (d), 128.2 (d), 128.1 (d), 119.6 (d), 109.1 (s), 82.1 (d), 75.8 (d), 74.5 (t), 73.1 (d), 66.1 (t), 26.4 (q), 25.3 (q); $|\alpha|_D$ +21.1 (c 0.956, $CHCl_3$)

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