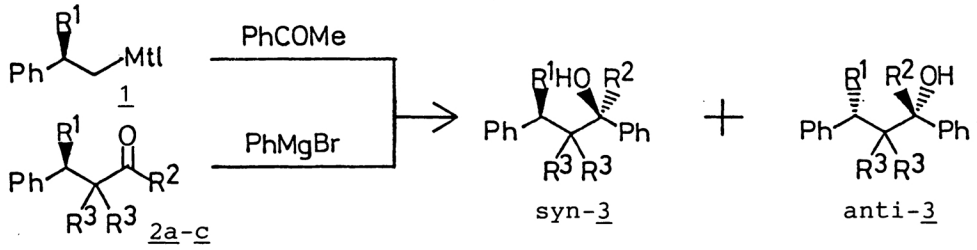
CHEMISTRY LETTERS, pp. 21-24, 1988.

1,3-Asymmetric Induction in Acyclic Systems by Practical Application of Dithioacetal Group

Yutaka HONDA,* Eitaro MORITA, Kimitaka OHSHIRO, and Gen-ichi TSUCHIHASHI†
Department of Chemistry, Faculty of Science and Technology, Keio University, 3-14-1, Hiyoshi, Kohoku-ku, Yokohama 223

2-Lithio-2-(1-methyl-2-alkenyl)-1,3-dithianes showed 1,3-syn-selectivity on addition to aldehydes. Moreover this selectivity could be increased up to 97 %de by using equilibration of potassium alkoxide of the adduct in the presence of a ligand.

It is very important to have methods for effective control of stereoselectivity in acyclic systems. 1,2-Asymmetric induction on C-C bond formation has made great progress. On the other hand, 1,3-asymmetric induction on C-C bond formation have been studied mainly by using cyclic intermediates or chelate complexes,[1] but there is not yet effective solution without using chelation control. For example, the addition of 1-metallo-2-substituted propane (1, R^1=Me, Mtl=MgBr or Li) to acetophenone showed a little selectivity (Eq. 1, R^2=Me, syn-3/anti-3=0.8-1.7). In the case of an addition of phenylmagnesium bromide to an β-substituted ketone (2a: R^1=R^2=Me, R^3=H), syn-selectivity was observed (Eq. 2, syn/anti=1.3-5.0).[2] The corresponding aldehyde (2b: R^1=Me, R^2=R^3=H) showed a little anti-selectivity (Eq. 2, syn/anti=1/1.1). Moreover the selectivity was slightly enhanced by the presence of bulky R^3 group (2c: R^1=Me, R^2=H, R^3=Me, syn/anti=1/1.4; 2d: R^1=Et, R^2=H, R^3=Ph, syn/anti=1/3.0).[3] These phenomena had been explained by using models of the transition states, which were placed in the least hindered configuration.

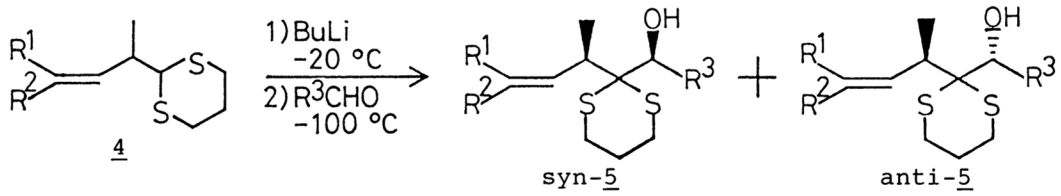


(1)

(2)

Since we were interested in the effect of an dithioacetal group on 1,3-asymmetric induction in acyclic systems, addition of carbanion[4] of 2-(1-methyl-2-alkenyl)-1,3-dithiane (4)[5] to various aldehydes in THF were examined (Eq. 3).

† Deceased on June 24, 1987.



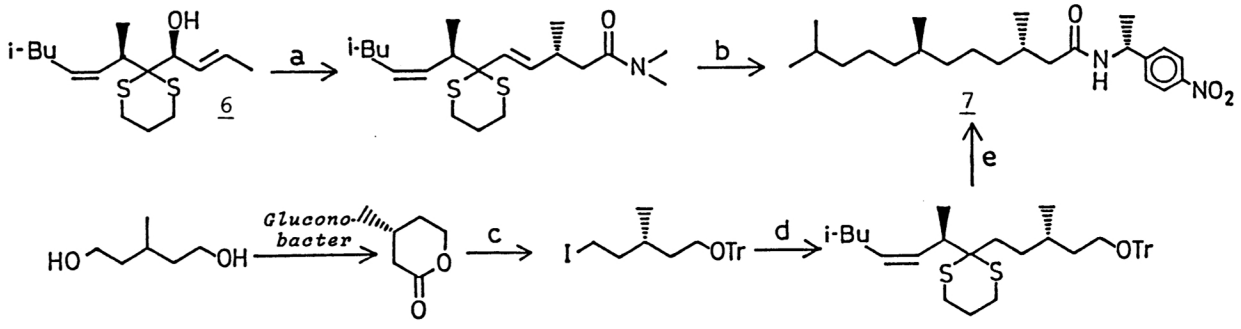
(3)

Table 1. Addition of 2-lithio-1,3-dithianes to aldehydes at -100 °C

Entry	R^1	R^2	R^3CHO	Additive	Yield/%	syn/anti[a]
1	H	H	PH⟨ ⟩CHO	-	92	9.4(6.1[b])
2	"	"	PHCHO	-	89	4.8
3	"	"	"	$BF_3 \cdot OEt_2$[c]	59	3.0
4	"	"	TMS, CHO	-	55	4.6
5	"	"	CHO	-	91	3.5
6	i-Bu	"	"	-	93	5.3
7	"	"	—≡—CHO	-	50	1.7

a) Determined by 400 MHz ^{1}H NMR. b) Reaction was carried out at -78 °C. c) $BF_3 \cdot OEt_2$ was added with the aldehyde.

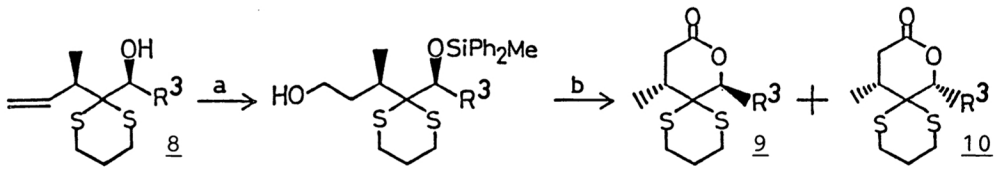
As summarized in Table 1, these additions showed syn-selectivity. The presence of a bulky substituent on the aldehydes gave an increased syn-selectivity in the following order: alkyl > phenyl > 1-silylalkenyl > alkenyl > alkynyl (entries 1,2,4,5,7). The bulkiness of R^1 groups resulted in an increased ratio (entries 5, 6). Activation of an aldehyde by $BF_3 \cdot OEt_2$ reduced the ratio (entry 3). Adduct (6, R^3=(E)-1-propenyl, entry 6) from crotonaldehyde was separated from its anti-isomer by preparative TLC as the corresponding diphenylmethylsilyl ether. Its relative stereostructure was determined by converting 6 into a known amide (7, 98 % de),[6] prepared via a Claisen rearrangement (Fig. 1).[6]



(a)$MeC(OMe)_2NMe_2$, 140 °C;(b)i)KOH,ii)CH_2N_2,iii)H_2/Ni,iv)KOH,v)$(COCl)_2$,vi)(R)-$NO_2C_6H_4CHMeNH_2$;(c)i)i-Bu_2AlH,ii)$HS(CH_2)_3SH$,$BF_3 \cdot OEt_2$,iii)TrCl-py,iv)NBS,$AgNO_3$,v)$NaBH_4$,vi)MsCl-py,vii)NaI,$NaHCO_3$;(d)4-BuLi;(e)i)AcOH,ii)BzCl-py,iii)H_2/Ni,iv)KOH,v)Swern oxidation,vi)CrO_3-H_2SO_4 in Me_2CO,vii)$(COCl)_2$,viii)(R)-$NO_2C_6H_4CHMeNH_2$.

Fig. 1. Determination of the relative structure of 6.

HPLC analysis[6] showed identical retention time with that of an authentic 7 (73 % de), prepared from 3-methyl-1,5-pentanediol through a selective oxidation by using *gluconobacter* IAM 1841.[7] Relative structures of adducts (8, R^3=Ph and $PhCH_2CH_2$, entries 1,2) were determined by 400 MHz ^1H NMR mesurement[8] of the corresponding lactones (9 and 10) respectively (Fig. 2).



8 9 10

(a)i)$Ph_2MeSiCl$,$Et_2{}^iPrN$,ii)BH_3·THF,iii)Me_3NO;(b)i)CrO_3-py,ii)Bu_4NF, HCl,pH7-8,iii)CrO_3-py.

Fig. 2. Determination of the relative structure of 8.

Lithium carbanion of the 1,3-dithiane will preferentially take an equatorial configuration, in which explanation by a stereoelectronically favorable p-d overlap or by a gauche effect were proposed.[9] Thus we considered that the conformation shown in Fig. 3 would be the least hindered, therefore addition to the aldehyde occurred from the fore side to give the syn-adducts preferencially.

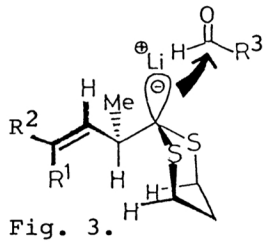
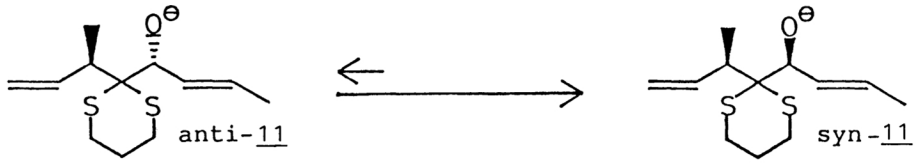


Fig. 3.

Moreover syn-anti equilibration[10] under the thermodynamic control[11] was examined. Treatment of the adduct (11, entry 5 in Table 1) with potassium hydride in the presence of ligand, HMPA or 18-crown-6, in THF (or HMPA) at rt showed a increase in the syn-selectivity up to 97 %de (Eq. 4, entries 4,5 in Table 2).



(4)

Table 2. Syn-anti equilibration under the thermodynamic control

Entry	KH/equiv.	Ligand(equiv.)	Solvent	Temp/°C	Time/h	Yield/%	syn/anti(%de)
1	1	-	THF	0	24	79	4.5 (64)
2	1	(HMPA)	HMPA-THF	0	24	100	4.2 (62)
3	1	18-crown-6(1.5)	THF	0	24	70	8.5 (79)
4	0.7	(HMPA)	HMPA	25	12	68	45.6 (96)
5	0.6	18-crown-6(1.0)	THF	25	16	81	65.5 (97)
6	0.7	" (1.0)	Toluene	25	12	100	4.9 (66)

We considered that the ratio of syn/anti increased via elimination-addition processes of crotonaldehyde, since the addition indicated in Fig. 3 was the most preferential. These methods are useful for a remote asymmetric induction in the syntheses of natural products.

References

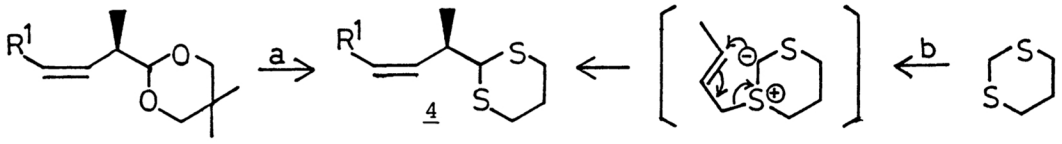
1) Recent review in 1,3-asymmetric induction on C-C bond formation; M. T. Reetz, *Angew. Chem., Int. Ed. Engl.*, 23, 556 (1984); T. W. Apsimon and T. L. Coller, *Tetrahedron*, 42, 5157 (1986); M. Braun, *Angew. Chem., Int. Ed. Engl.*, 26, 24 (1987); and references cited therein.

2) T. J. Leitereg and D. J. Cram, *J. Am. Chem. Soc.*, 90, 4011 (1968).

3) M. Brienne, C. Quannes, and J. Jacques, *Bull. Soc. Chem. Fr.*, 1968, 1036.

4) The corresponding 2-silyl-1,3-dithiane showed no selectivity by the treatment with aldehydes in the presence of tetrabutylammonium fluoride in THF.

5) Chiral 4 (R^1=i-Bu, >98 %ee) was prepared from methyl (R)-lactate[12] via a reductive 1,2-rearrangement and an acetal exchange.[13] Racemic 4 (R^1=H) as a simple model was prepared via a [2,3]-sigmatropic rearrangement[14] from 1,3-dithiane and crotyl bromide.



(a) $HS(CH_2)_3SH, BF_3 \cdot OEt_2$; (b) i)(E)-1-bromo-2-butene, ii)BuLi.

6) K. K. Chan, N. Cohen, J. P. D. Noble, A. C. Specian, and G. Sauay, *J. Org. Chem.*, 41, 3497 (1976). Relative structure of 7 was determined by HPLC analysis by using Develosil (Nomura Chemical Co., LTD.); hexane/ethyl acetate=4/1 (v/v), flow rate 1.0 ml/min, k'_{3S}=13.05, $\alpha = k'_{3R}/k'_{3S}$=1.26.

7) H. Ohta, H. Tetsukawa, and N. Noto, *J. Org. Chem.*, 47, 2400 (1982).

8) ^{1}H NMR ($CDCl_3$); 9 [R^2=Ph, Eu(fod)$_3$ 0.13 equiv.]: δ 2.69 (ddq, 1H, $J_{2ax,3eq}$= 6.84 Hz, $J_{2eq,3eq}$=5.86 Hz, $J_{3,3'}$=6.83 Hz, H-3) ppm. 10 (R^2=Ph): δ 2.32 (ddq, 1H, $J_{2ax,3ax}$=11.72 Hz, $J_{2eq,3ax}$=7.32 Hz, $J_{3,3'}$=6.34 Hz, H-3) ppm.

9) E. L. Eliel, A. A. Hartmann, and A. G. Abatjoglou, *J. Am. Chem. Soc.*, 96, 1807 (1974).

10) Threo-erythro equilibration of aldol products had been reported; C. H. Heathcock, C. H. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, and J. Lampe, *J. Org. Chem.*, 45 1066 (1980).

11) Thermodinamic control by using a spiroketalization had been reported; S. L. Schreiber and Z. Wang, *J. Am. Chem. Soc.*, 107, 5303 (1985).

12) Enantiomeric excess of methyl (R)-lactate was determined to be over 98 %ee by HPLC analysis of the corresponding (R)-MTPA ester.

13) Y. Honda, M. Sakai, and G. Tsuchihashi, *Chem. Lett.*, 1985, 1153.

14) E. Hunt and B. Lythgoe, *J. Chem. Soc., Chem. Commun.*, 1972, 757.

(Received September 12, 1987)