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1,3-Anti Asymmetric Induction in Addition of Organotitanium Reagents to β-Substituted Aldehydes with a Dithioacetal Group

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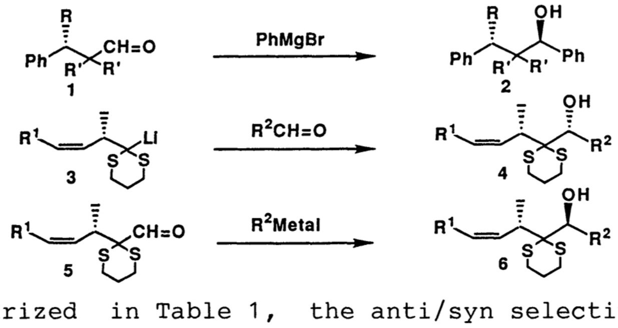
β-Substituted aldehydes with a dithioacetal group at α-position realized remarkable 1,3-anti selectivity in addition of organotitanium reagents in acyclic systems.

1,3-Asymmetric induction on C-C bond formation in acyclic systems has mainly been rationalized by using chelate transition state models.[1] Unfortunately, there is not yet effective solution in the case of β-substituted aldehydes. For example, an addition of Grignard reagent to a β-substituted aldehyde (**1**) proceeded with a low anti-selectivity (Eq. 1, R=Me, R'=H, syn-**2**/anti-**2**=1/1.1),[2] which is slightly enhanced in the presence of alkyl groups at α-position (Eq. 1, R=R'=Me, syn-**2**/anti-**2**=1/1.4; R=Et, R'=Ph, syn-**2**/anti-**2**=1/3.0).[3] We have previously reported the achievement of meaningful 1,3-syn selectivity (syn-**4**/anti-**4**=1.7-9.4) in addition of 2-lithio-2-(1-methyl-2-alkenyl)-1,3-dithianes (**3**) to various aldehydes (Eq. 2), moreover the diastereo excess of **4** [R^2=(E)-1-propenyl] could be increased up to 97 %de under equilibration of potassium salt with ligand.[4] A dithioacetal group is usefull for conversion into a methylene group and a carbonyl group. Meanwhile, we were interested in the effect of a dithioacetal group to anti-selectivity on 1,3-asymmetric induction in acyclic systems, the addition of organometallic reagents to β-substituted aldehydes (**5**)[5] has been studied (Eq. 3).



(1)

(2)

(3)

As summarized in Table 1, the anti/syn selectivity[6] using methylmagnesium bromide as a nucleophile was low and it depended on the solvent used (Entries 1-3). The Lewis acidity of a metal, which was influenced by the affinity of a solvent, resulted in an increasing of the selectivity. Organotitanium reagents were next examined in the hope of high anti-selectivity. As the result, the reaction of **5** with $MeTiCl_3$[7] in CH_2Cl_2 gave anti-**6** predominantly (Entries 5,8,9). It is likely that free rotation of formyl group is limited by chelation of titanium to the carbonyl group and the sulfur atom, and another reagent attacked from a less-

Table 1. Addition of organometallic reagents to **5**

Entry	R^1	R^2	Reagent (equiv.)	Solvent	Temp/°C	Time/h	Yield/%	anti/syn
1	H	Me	MeMgBr (1.3)	Et_2O	-78	2	52	73 / 27
2	$Ph(CH_2)_3$	Me	" (1.2)	"	-78	2	98	58 / 42
3	$Ph(CH_2)_3$	Me	" (5.0)	THF	-78	20	33	32 / 68
4	$Ph(CH_2)_3$	Me	MeLi (2.0)	"	-78	1.5	98	57 / 43
5	H	Me	$MeTiCl_3$ (10.0)	CH_2Cl_2	-78 → 0	0.5	72	98 / 2
6	H	Me	$MeTiCl_3 \cdot OEt_2$ (4.2)	"	-30 → 0	2	72	83 / 17
7	H	Me	$MeTiCl_2(OIp)$ (4.1)	"	-20	1	77	98 / 2
8	$Ph(CH_2)_3$	Me	$MeTiCl_3$ (10.0)	"	-78 → 0	1.5	81	96 / 4
9	$Ph(CH_2)_3$	Me	" (10.0)	"	0	0.5	98	96 / 4
10	$Ph(CH_2)_3$	Me	$MeTiCl_3 \cdot OEt_2$ (3.0)	"	-30 → 0	4	75	99 / 1
11	$Ph(CH_2)_3$	Me	" (3.0)	"(+Et_2O)	-30 → 0	3	18	97 / 3
12	$Ph(CH_2)_3$	Me	$TiCl_4$(4)-MeMgBr(1)	CH_2Cl_2	0	0.5	65	83 / 17
13	$Ph(CH_2)_3$	Me	$MeTiCl_2(OIp)$ (3.9)	"	-20	1	100	>99 / 1
14	$Ph(CH_2)_3$	∿	∿MgBr (1.5)	Et_2O	-78	1	100	58 / 42
15	$Ph(CH_2)_3$	∿	$TiCl_4$-∿TMS(10.0)	CH_2Cl_2	-78 → 15	2	25	73 / 27
16	$Ph(CH_2)_3$	∿	$TiCl_4$-∿TMS(10.0)	"	0	1.5	44	65 / 35
17	$Ph(CH_2)_3$	∿	∿$TiCl_3 \cdot OEt_2$ (3.0)	"	-30 → 0	1.5	38	50 / 50

hindered site of a transition state (Fig. 1). $MeTiCl_3 \cdot OEt_2$[8)] increased the anti-selectivity in the presence of R^1 group (Entry 10), but an addition of excess of diethyl ether reduced the selectivity (Entry 11). It was considered that a ratio of chelation to non-chelation decreased, because the equilibrium shifted from mono-etherate to bis-etherate[9)] which was incapable to chelate. Treatment of **5** with $TiCl_4$ and then MeMgBr showed a reduced selectivity (Entry 12). It was concluded that the bulkiness of reagent was needed as well as the Lewis acidity. Indeed, $MeTiCl_2(OIp)$[10)] gave the best result (Entries 7, 13), since the Lewis acidity decreases and the bulkiness increases in going from $MeTiCl_3$ to $MeTiCl_2(OIp)$. Addition of allylsilane with $TiCl_4$ to **5** showed a low yield and a little increased selectivity (Entries 14-16), since the reagent was less stable at the reaction temperature. Allyltitanium reagent[11)] showed no selectivity (Entry 17).

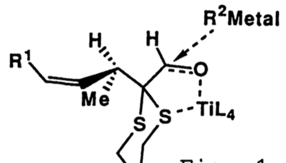


Fig. 1.

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References

1) Recent review in 1,3-asymmetric induction on C-C bond formation; M. T. Reetz, "Reactivity and structure concepts in organic chemistry," Springer-verlag (1986), Vol. 24; 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).
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4) Y. Honda, E. Morita, K. Ohshiro, and G. Tsuchihashi, *Chem. Lett.*, 1988, 21.
5) (S)-Aldehyde (**5**) was prepared from (S)-**3**[4)] in 86% yield by treatment with N,N-dimethylformamide in THF at -78 °C, and (R)-**5** can be prepared analogously.
6) The relative structure and the ratio of **6** were determined by 400 MHz ^{1}H NMR.[4)]
7) Prepared from $TiCl_4$ (in CH_2Cl_2) and Me_2Zn (in hexane) at -20 °C.
8) Prepared from $TiCl_4$ and MeMgBr (in Et_2O) at -30 °C.
9) M. T. Reetz, S. H. Kyung, and M. Hullmann, *Tetrahedron*, 42, 2931 (1986).
10) Prepared from $TiCl_3(OIp)$ (in CH_2Cl_2) and Me_2Zn at -20 °C.
11) Prepared from $TiCl_4$ and allylmagnesium bromide (in Et_2O) at 0 °C.

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