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1,2-Asymmetric Induction on Conjugate Addition to Chiral γ-Substituted-α,β-unsaturated Aldehyde

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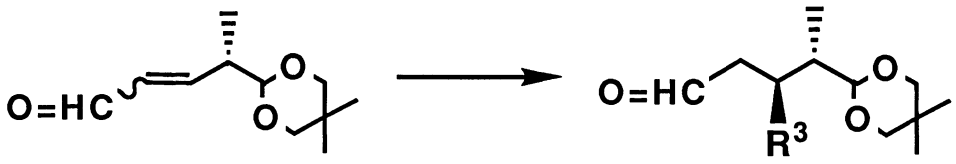
The conjugate addition of organo-cuprate and -copper reagents to chiral γ-substituted-α,β-unsaturated aldehydes yields the anti-adducts predominantly.

The construction of the adjacent tertiary carbons is a important problem for total synthesis of natural products. Remote asymmetric induction on cujugate addition in acyclic systems has been investigated by using metalated hydrazone[1] and amide enolate.[2] Meanwhile, 1,2-asymmetric induction biased by the chirality at γ-substituents of α,β-unsaturated aldehydes is a promising procedure for obtainment of the high optical activity, if such substrates are readily available. We had previously reported an access to chiral α-substituted-β,γ-unsaturated acetals by using reductive 1,2-rearrangement of chiral α-sulfonyloxy acetals.[3] 1,2-Asymmetric induction on conjugate addition to γ-alkoxy-α,β-unsaturated carbonyl compounds has been widely investigated,[4] but one to γ-alkyl- α,β-unsaturated derivatives have a little reported.[5] Recentry Yamamoto et al. have reported that the conjugate addition of γ-phenyl-α,β-unsaturated esters have been controlled by choice of the type of organocopper reagents and the double bond geometry.[6]

We have interest in the control of stereo- and regio-selectivities by the use of the cyclic acetal group in acyclic systems. Anti-selective epoxidation governed by chelation control of metal with acetal group[7] and stereoselective bromohydrin formation by using the steric hindrance of the acetal group[8] have been reported. Therefore, we have studied 1,2-asymmetric induction on conjugate addition of γ-substituted-α,β-unsaturated aldehydes in the hope of the anti-selectivity (Eq. 1).



(1)

Chiral (E)-unsaturated alcohol (**2a**, >99 %ee) had been prepared by a reductive 1,2-rearrangement of chiral mesyrate (**1a**)[9] accompanied with deprotection of the trityl group.[10] Treatment of **2a** with activated MnO_2[11] in hexane at rt gave (E)-unsaturated aldehyde (**3a**) quantitatively without racemization (Fig. 1). (Z)-Unsaturated aldehyde (**3b**) was prepared by the anologous procedure. Treatment of **3a** with some organo-cuprate and -copper reagents under various conditions gave 1,4-

adducts (4) and 1,2-adducts (5) (Table 1).

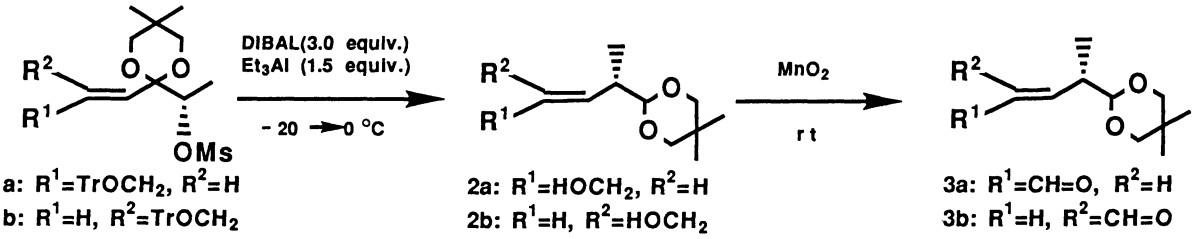
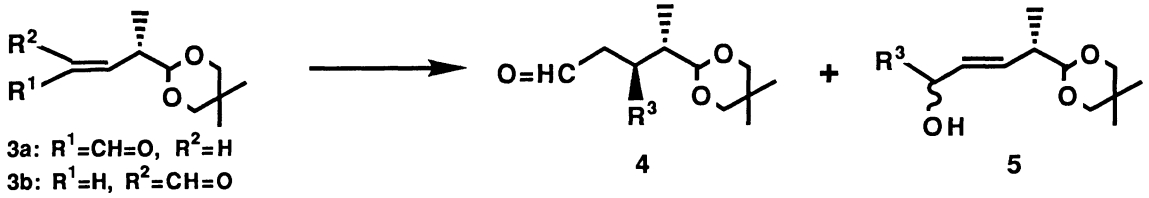


Fig. 1. Preparation of chiral unsaturated aldehyde (3).

Table 1. Conjugate addition of organo-cuprate and -copper reagents to 3



Entry	3	R^3	Reagent (equiv.)	Additive (equiv.)	Activator (equiv.)	Solv.	Temp/°C (Time/h)	1,4[a] /1,2	Yield of 4/%	anti[a] /syn
1	E	Me	Me_2CuLi[b] (1.1)	-	-	Et_2O	0 (2)	96/4	96	72/28
2	E	"	"[b] (1.1)	-	-	"	-78→0(2)	96/4	82	80/20
3	E	"	"[c] (1.1)	LiBr(2.2)	-	"	" (2)	99/1	20	66/34
4	E	"	"[b] (1.1)	-	TMSCl(2)	"	" (2)	96/4	87	84/16
5	E	"	"[b] (1.1)	-	" (2)	THF	" (1)	27/73	18	77/23
6	E	"	"[b] (1.1)	-	$BF_3 \cdot OEt_2$(2)	Et_2O	"(0.5)	38/62	38	76/24
7	E	"	"[b] (1.1)	Bu_3P(1.2)	TMSCl(2)	"	" (2)	96/4	79	85/15
8	E	Bu	"[b] (1.1)	" (1.2)	" (2)	"	" (2)	96/4	44	83/17
9	Z	Me	"[b] (1.1)	" (1.2)	" (2)	"	" (2)	98/2	63	67/33
10	E	"	"[b] (1.1)	HMPT(1.0)	" (2)	"	" (1)	34/66	34	92/8
11	E	"	"[b,d] (1.1)	TMEDA(1.0)	" (2)	"	" (1)	94/6	94	78/22
12	E	"	MeCu[b] (1.1)	Bu_3P(1.2)	" (2)	"	" (2)	99/1	26	82/18
13	E	"	"[b] (1.1)	TMEDA(3.0)	" (2.5)	THF	-78(1)	56/44	29	85/15
14	E	"	"[g] (1.9)	HMPT(2.0)	" (2)	"	" (3)	>99/1	91	82/18
15	E	Bu	BuCu[g] (1.9)	" (2.0)	" (2)	"	" (3)	>99/1	16	78/22
16	E	Me	$Me_2CuMgBr$[e] (1.1)	Bu_3P(1.2)	" (2)	Et_2O	" (2)	< 1/99	0	-
17	E	"	MeMgBr(Cu cat)[f]	HMPT(2.0)	" (2)	THF	-78(3)	24/76	23	94/6
18	E	"	$Me_2CuMgBr$[g] (1.5)	HMPT(2.1)	" (2)	"	" (3)	97/3	97	84/16
19	Z	"	"[g] (1.5)	" (2.1)	" (2)	"	" (3)	73/27	72	69/31
20	E	Bu	$Bu_2CuMgBr$[g] (1.5)	" (2.1)	" (2)	"	" (3)	>99/1	68	84/16

a) Determined by 400 MHz ^1H NMR. b) Prepared from MeLi (salt free in Et_2O) and CuI (unpurified) at -10 °C. c) Prepared from MeLi (with LiBr) and CuI. d) Deprotected by KF-MeOH-H_2O. e) Prepared from MeMgBr and CuI. f) Prepared from MeMgBr (1.9 equiv.) and CuBr·Me_2S (0.6 equiv.). g) Prepared from R^3MgBr and CuBr·Me_2S at -50 °C.

Addition of Me_2CuLi to **3a** in Et_2O under usual conditions gave anti-adduct (**4**) predominantly (Entries 1 and 2).[12] Chlorotrimethylsilane (TMSCl), which strongly accelerates the conjugate addition,[13] enhances the anti-selectivity (Entry 4), and further enhances the selectivity in the presence of Bu_3P as an additive (Entry 7). Me_2CuLi-BF_3 reagent gives low regio- and stereo-selectivities (Entry 6). The combination of hexamethylphosphoric triamide (HMPT) and TMSCl is known to be an accelerator for conjugate addition of the stoichiometric lithium cuprate[14] and for the copper-catalized conjugate addition of the Grignard reagent.[15] These addition show high anti-selectivities, but 1,2-addition proceeds predominantly (Entries 10 and 17). The anti-selectivity is reduced in the presence of lithium salt (Entry 3), but the salt free alkyllithium is not available. Since the Grignard reagent is available from various alkyl halides without a salt, it is more useful than the lithium cuprate. Addition of the stoichiometric cuprate, which was prepared from the Grignard reagent, with HMPT and TMSCl shows good regio- and stereo-serectivities (Entries 18 and 20). The combination of TMSCl and tetramethylethylenediamine (TMEDA), which is also reported as an accelerator,[16] shows a low regio-selectivity in addition of lithium cuprate and methylcopper (Entries 11 and 13). The choice of the solvent was a important factor (Entries 4, 5, 16, and 17). The organocuprate reagents show better stereo-selectivity than the organocopper reagents. Treatment of (Z)-unsaturated aldehyde (**3b**) under the conditions employed in entries 7 and 18 gave low anti-selectivities (Entries 9 and 19). It is considered that the reagent attacks from a less-hindered site of the more stable transition state (**A**),[17] in which the acetal group locates opposite to the alkenyl group for the steric repulsion, to yield anti-**4** (Fig. 2). Otherwise, existence of the less stable transition state (**B**) increases by the chelation of metal to the acetal group and the carbonyl group. The chelation would be easily occured in the case of **3b** (Fig. 2).

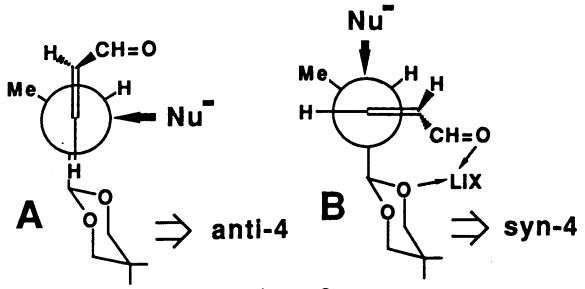


Fig. 2.

Typical procedure for the treatment of **3** with Grignard reagent is as follows: Grignard reagent (3.0 equiv.) is added into a mixture of CuBr (1.5 equiv.) and Me_2S (1.5 equiv.) in THF at -50 °C. After 1 h, HMPT (2.1 equiv.) in THF is added to the mixture at -78 °C. After 10 min, TMSCl (2.0 equiv.) and **3** in THF are added successively. Immediately, the color of the mixture changes to yellow. After 3 h, the mixture is quenched by saturated aqueous NH_4Cl, and allows to warm to room temperature. The solution is extracted with ethyl acetate. The organic layer is washed by brine and dried over $MgSO_4$. Concentration of the extract gives a TMS enol ether of **4**. This is treated with K_2CO_3 (0.1 M) in MeOH at 0 °C for 20 min to yield an aldehyde (**4**). It is purified by silica-gel column chromatography.

The resulting anti-adduct (**4**), which can be purified to >99 %de by silica-gel column chromatography, is a useful bifunctional chiral template. The application of the present results to the synthesis of natural products is under current investigation. This work is financially supported from the Ministry of Education, Science and Culture of Japan.

References

1) D. Enders, K. Papadopoulos, B. E. M. Rendenbach, R. Appel, and F. Knoch, *Tetrahedron Lett.*, 27, 3491 (1986).

2) M. Yamaguchi, K. Hasebe, S. Tanaka, and T. Minami, *Tetrahedron Lett.*, 27, 959 (1986).

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

4) Y. Yamamoto, S. Nishii, and T. Ibuka, *J. Chem. Soc., Chem. Commun.*, 1987, 464, and references cited therein. For related hetero conjugate addition, see M. Isobe, M. Kitamura, and T. Goto, *Tetrahedron Lett.*, 1979, 3465.

5) D. Kruger, A. E. Sopchik, and C. A. Kingsbury, *J. Org. Chem.*, 49, 778 (1984); C. H. Heathcock and D. E. Uehling, *ibid.*, 51, 279 (1986).

6) Y. Yamamoto, S. Nishii, and T. Ibuka, *J. Chem. Soc., Chem. Commun.*, 1987, 1572; Y. Yamamoto, S. Nishii, and T. Ibuka, *J. Am. Chem. Soc.*, 110, 617 (1988).

7) Y. Honda, A. Ori, and G. Tsuchihashi, *Chem. Lett.*, 1986, 1417.

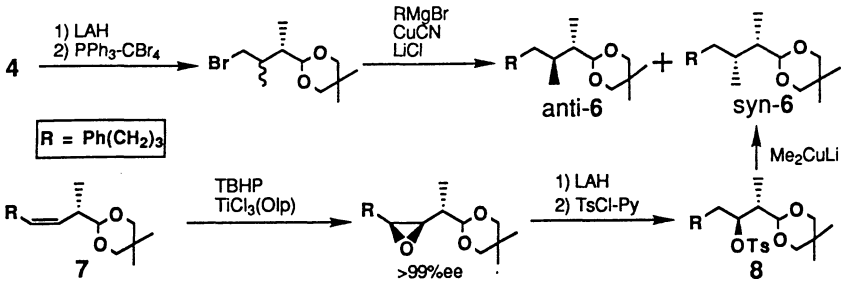
8) Y. Honda, Y. Kataoka, M. Unno, and G. Tsuchihashi, *Chem. Lett.*, 1987, 2133.

9) Chiral mesylate (**1**) was prepared from (S)-O-(1-ethoxyethyl)-N,N,-dimethyl-lactamide by treatment with lithium 3-(tetrahydropyranyl)oxy-1-propyn-1-ide followed by acetalization, hydrogenation, and mesylation.[3]

10) Trityl group can be easily deprotected by combination of Et_3Al and DIBAL without destruction of the cyclic acetal group. It is considered that Et_3Al activates the oxygen atom with trityl group as a Lewis acid, and then a hydride attacks to the trityl group to yield a triphenylmethane quantitatively.

11) E. J. Corey, N. W. Gilman, and B. E. Ganem, *J. Am. Chem. Soc.*, 90, 5616 (1968).

12) The relative stereochemistry was determined by conversion of **4** into known anti-**6**.[18] The ^1H NMR of minor component was identical with that of an authentic syn-**6**, prepared from Z-alkene (**7**) through anti-epoxidation[7] and substitution reaction of the tosylate(**8**) by methyl group.[19]



13) E. J. Corey and N. W. Boaz, *Tetrahedron Lett.*, 27, 6015 (1985); *ibid.*, 27, 6019 (1985).

14) E. Nakamura, S. Matsuzawa, Y. Horiguchi, and I. Kuwajima, *Tetrahedron Lett.*, 27, 4029 (1986).

15) Y. Horiguchi, S. Matsuzawa, E. Nakamura, and I. Kuwajima, *Tetrahedron Lett.*, 27, 4025 (1986).

16) C. R. Johnson and T. J. Marren, *Tetrahedron Lett.*, 28, 27 (1987).

17) A modified Felkin-Anh model,[6] which may be destabilized owing to steric repulsion, also produce anti-**4** predominantly.

18) C. A. Henrick, *Tetrahedron*, 33, 1845 (1977).

19) C. R. Johnson and G. A. Dutra, *J. Am. Chem. Soc.*, 95, 7783 (1973).

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