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CHIRAL ALCOHOL-INDUCED DIASTEREOSELECTIVE CONJUGATE ADDITION AND CYCLIZATION

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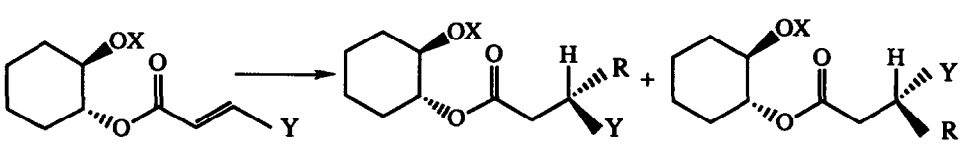
Abstract: Conjugate addition of organocuprate reagents to α,β-unsaturated esters of chiral *trans*-cyclohexanediol proceeded diastereoselectively, and the intramolecular trapping of the generated enolate also afforded asymmetric cyclization products.

Conjugate addition of organocuprate reagents to α, β-unsaturated ketones or esters is a convenient procedure in the carbon-carbon bond formation.[1] For this conjugate addition to be applied widely in the solution of stereochemical problems in the synthesis of natural products, it should desirably proceed in a stereoselective manner.[2]

We now wish to describe the diastereoselective conjugate addition of organocuprates to mono-α,β-unsaturated esters of (1*R*, 2*R*)-1, 2-cyclohexanediol[3] (**1**) (scheme 1), and the asymmetric cyclization *via* the intramolecular trapping of the resulting enolate (scheme 2)

Substrates (**2**) were prepared by monoesterification of **1** with α,β-unsaturated acid chlorides. Results of 1,4-addition are summarized in Table 1. Better results in the diastereoselectivity were obtained in the case of diorganocuprate as shown in entry 1-7,[4] and the best was 94 : 6 (entry 1, 2). 1,4-Addition using $BuCuBF_3$ (entry 8) or BuMgBr (entry 9) resulted in low diastereoselectivity and poor yield. It is noteworthy that 1,4-addition of BuLi (entry 10) or PhLi (entry 12) afforded the other diastereomer, suggesting that 1,4-addition of organolithium proceeds in a clearly different manner from that of organocuprate. In the case of the tosylate (entry 11), diastereoselectivity was not observed. Absolute stereochemistry of 1,4-addition products was determined by comparison[5] with the known compounds.

Scheme 1



2 **3a-8a** **3b-8b**

The above findings suggest that the intramolecular alcohol plays an important role for the formation of certain complex between substrate and diorganocuprate.

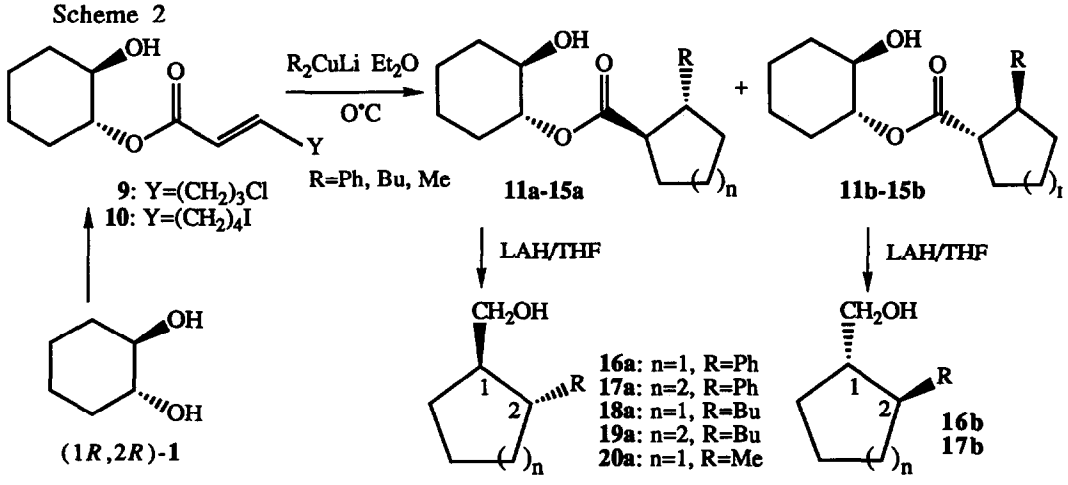
Table 1. Diastereoselective 1,4-addition to 2

Entry	Substrates (2)		Reagents	Reac.	Cond.	Products				Yield	Abs.*2	Diast.Ratio*4
	X	Y		°C	hour		X	Y	R	(%)	Config.	(a : b)
1	H	Me	Ph_2CuLi	-50	0.5	3	H	Me	Ph	61	*R*	94 : 6(95:5)*5
2	H	Me	Ph_2CuLi	-30	0.5	3	H	Me	Ph	66	*R*	94 : 6
3	H	Me	Ph_2CuLi	0	0.5	3	H	Me	Ph	63	*R*	93 : 7
4	H	Ph	Me_2CuLi	-30	0.5	4	H	Ph	Me	71	*S*	92 : 8
5	H	Et	Ph_2CuLi	-30	0.5	5	H	Et	Ph	63	*R*	86 : 14
6	H	Me	Bu_2CuLi	-30	0.5	6	H	Me	Bu	91	*S**3	86 : 14*6
7	H	Ph	Bu_2CuLi	-30	0.5	7	H	Ph	Bu	79	*S*	91 : 9(92:8)
8	H	Ph	$BuCuBF_3$	-78	1.0	7	H	Ph	Bu	33	*S*	63 : 38
9	H	Ph	BuMgBr	-78	1.0	7	H	Ph	Bu	15*1	*S*	69 : 31
10	H	Ph	BuLi	-78	1.0	7	H	Ph	Bu	20	*R*	16 : 84(14:86)
11	Ts	Me	Ph_2CuLi	-30	0.5	8	Ts	Me	Ph	50	-	51 : 49*7
12	H	Et	PhLi	-78	1.0	5	H	Et	Ph	31	*S*	9 : 91

*1) Starting material was recovered in 43% yield. *2) Absolute configuration of the major diastereomer. *3) This inversion of configuration is only due to the CIP selection rules and not to the steric course of the reaction.*4) Diastereomer ratio was measured by 270 MHz ^{1}H-NMR of MTPA ester [(*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid ester] of the 1,4-adducts except for **6** (entry 6) and **8** (entry 11). *5) Values in parentheses were obtained by analysis of ^{13}C-NMR spectroscopy of the 1,4-adducts.*6) This value was calculated on the basis of specific rotation of reduction product.[5] *7) Diastereomer ratio was determined by the ^{1}H-NMR.

Next we undertook the asymmetric cyclization by intramolecular trapping [6] of the enolate generated by the remote chiral alcohol-induced 1,4-addition. Reaction of 6-chloro-2-hexenoate (**9**)[7] with Ph_2CuLi at -30°C afforded only 1,4-addition products, and no cyclized product was detected. However, reaction at 0°C afforded

Scheme 2



the cyclized products **11a** and **11b**[4] in 44% and 6% yields, respectively. Similar reactions proceeded with high diastereoselectivity to give five- and six-membered rings as shown in Scheme 2 and Table 2.

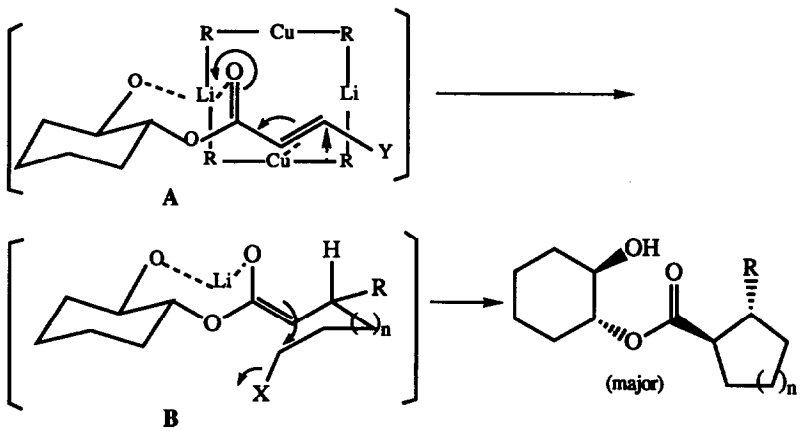
Table 2 Construction of chiral 1, 2-disubstituted cyclic compounds

Entry	Substrates	n	R	Cyclized Products (yield, %)*1)		Diast. Ratio (a:b)
1	**9**	1	Ph	**11a** (44)	**11b** (6)	88 :12
2	**10**	2	Ph	**12a** (54)	**12b** (7)	89 :11
3	**9**	1	Bu	**13a** (46)	**13b** (5)	90 :10
4	**10**	2	Bu	**14a** (15)	*2)	
5	**9**	1	Me	**15a** (50)	**15b** (7)	88 : 12

*1) Yields isolated by flash column chromatography. *2) Not isolated

Two substituents of cyclized products were determined to be *trans*-configuration by analysis of the nuclear Overhauser effect difference spectra (NOEDS) between C_2-H and C_1-CH_2OH of reduction products **16a,b** and **17a**, in addition to coupling constant (J=11Hz) of C_1-H and C_2-H of **17a,b**. Absolute stereochemistry[8] of the cyclized products was determined by comparison with the known compounds. This one-pot asymmetric cyclization seems to be a practical procedure because each cyclized diastereomer could be easily separated by column chromatography on silica gel.

Scheme 3



The stereochemical course of these conjugate additions and subsequent cyclizations by organocuprate may be rationalized *via* the transition states illustrated in Scheme 3. Assumptions of *s-cis* configuration for substrate and the square-planar dimeric structure[1a] for the cuprate allow us to consider that a sequence of these reactions starts from chelation of lithium ion with ester carbonyl and alcohol; this is followed by spontaneous formation of the copper(I)-alkene π-complex, and then a shift of R-substituent to the double bond from *re*-face in a stereo-controlled manner (**A**). Subsequently, the cyclized product may be obtained diastereoselectively *via* the intramolecular alkylation from *re*-face of the resulting enolate (**B**).

References and Notes

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2. a) G. H. Posner, An introduction to synthesis using organocopper reagent, Wiley, New York, 1980; b) J. F. Normant and A. Alexais, "Current Trends in Organic Synthesis", Pergamon Press, New York, 291 (1983).
3. Z.-F. Xie, I. Nakamura, H. Suemune and K. Sakai, *J. Chem. Soc., Chem. Commun.*, **1988**, 966.
4. All compounds obtained in this manner gave satisfactory spectroscopic data. Selected spectroscopic data for representative products are as follows. **11a** (n=1, R=Ph): IR (neat): 3450, 1725, 1600, 1180 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.85 (1H, m, CHCO), 3.18 (1H, m, CHPh), 3.30 (1H, m, HC-O), 4.41 (1H, m, CHOCO), 7.24 (5H, m, aromatic-H). MS (*m/z*): 288 (M^+), 190, 144, 118. $[\alpha]_D^{26}$ -148.3° (c=0.12, $CHCl_3$). **11b** (n=1, R=Ph): IR (neat): 3450, 1725, 1600, 1175 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.86 (1H, m, CHCO), 3.28 (1H, m, CHPh), 3.43 (1H, m, HC-O), 4.48 (1H, m, CHOCO), 7.25 (5H, m, aromatic-H). MS (*m/z*): 288 (M^+), 190, 144, 118. $[\alpha]_D^{24}$ +45.9° (c=1.15, $CHCl_3$). **16a** (n=1, R=Ph): IR (neat): 3350, 1600, 1020 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.68 (1H, ddd, J=9.40, 9.40, 7.98 Hz, CHPh), 3.50 (1H, dd, J=10.56, 6.93 Hz, HC-O), 3.63 (1H, dd, J=10.56, 5.28 Hz, HC-O), 7.24 (5H, m,aromatic-H). MS (*m/z*): 176 (M^+), 158, 143, 117. $[\alpha]_D^{27}$ -37.3° (c=1.9, $CHCl_3$).
5. Hydrolysis of **4** with 1% $NaOH/H_2O$ provided the optically active (*S*)-(+)-3-phenylbutyric acid: $[\alpha]_D^{26}$ +37.5° (c=2.5,benzene). [see P. A. Levene and R. E. Marker, *J. Biol. Chem.*, **93**, 761 (1931): (*R*)-(-)-3-phenylbutyric acid, reported value $[\alpha]_D$ -47.92° (benzene)]. Reduction of **6** with $LiAlH_4$/THF afforded (*S*)-(-)-3-methyl-1-heptanol: $[\alpha]_D^{26}$ -2.18° (c=1.1,CH_2Cl_2). [see P. A. Levene and A. Rothen, *J. Org. Chem.*, **76**, 1 (1936): (*S*)-(-)-3-methyl-1-heptanol, $[\alpha]_D$ -3.07° (neat)]. In the (+)-MTPA ester of **4** (*S*-configuration is major), methoxy signals with relative intensity of 11 to 1 were observed at δ 3.51 and δ 3.42, respectively. On the other hand, those of **3** (*R*-configuration is major) were observed at δ 3.51 and δ 3.42 with reverse relative intensity of 1 to 15. Based on the above findings that, in this series, the methoxy signal in 3*R*-isomer was observed at a higher field than that of 3*S*-isomer, absolute configurations of **5a,b** and **7a,b** were determined as shown in Table 1.
6. G. H. Posner, J. J. Sterling, C. E. Whitten, C. M. Lentz and D. J. Brunelle, *J. Am. Chem. Soc.*, **97**, 107 (1975).
7. (*E*)-6-Chloro-2-hexenoyl chloride and (*E*)-7-iodo-2-heptenoyl chloride were prepared by Wittig-Horner reaction of $(EtO)_2P(O)CH_2COOEt$/NaH with ω-haloaldehyde, obtained by PCC oxidation of the corresponding alcohols, followed by hydrolysis (1% NaOH) and subsequent treatment with $SOCl_2$.
8. Absolute configuration of cyclized products was determined as follows. PCC oxidation of **16a**, obtained by $LiAlH_4$ reduction of **11a**, afforded (1*R*, 2*R*)-(-)-1-formyl-2-phenylcyclopentane, $[\alpha]_D^{26}$ -76.0° (c=1.9, benzene), [see I. Hashimoto, H. Kogen, K. Tomioka and K. Koga, *Tetrahedron Lett.*, **20**, 3009 (1979): reported value, $[\alpha]_D$ -76.8°(benzene)]. Hydrolysis of **12a** with 1% $NaOH/H_2O$ afforded (1*R*,2*R*)-(-)-2-phenylcyclohexanecarboxylic acid, $[\alpha]_D^{20}$ -63.2°(c=1.1, MeOH), [see L. Vervit and H. C. Price, *J. Am. Chem. Soc.*, **101**, 5143 (1972): (1*S*,2*S*)-(+)-2-phenylcyclohexanecarboxylic acid, reported value, $[\alpha]_D^{26}$+68 °(MeOH)].

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