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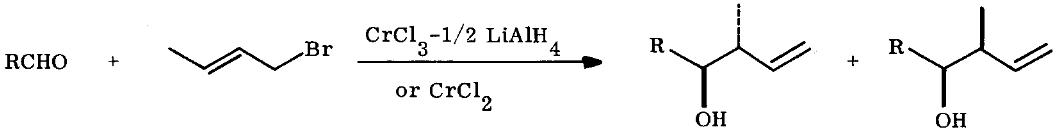
CHROMIUM(II) MEDIATED THREO SELECTIVE SYNTHESIS OF HOMOALLYL ALCOHOLS

Tamejiro Hiyama,* Keizo Kimura, and Hitosi Nozaki

Department of Industrial Chemistry, Kyoto University, Yoshida, Kyoto 606, Japan

Remarkable threo selectivity is observed in the reaction of aldehydes with trans- and cis-1-bromo-2-butene with the aid of chromium(II) salts. Solvent effect as well as the synthetic application is discussed.

How to attain acyclic stereoselection is of great importance in modern synthetic methodologies. A solution to this end may be presented by use of a variety of metals as the gegen ion of carbanion species.[1] In this sense chromium(II) mediated Barbier-Grignard reaction of allyl halides with aldehydes or ketones exhibits remarkable feature:[2] 1-bromo-2-butene and benzaldehyde give only one diastereomer of 2-methyl-1-phenyl-3-buten-1-ol whose stereochemistry has been determined to be threo by Heathcock and his coworker.[3] We wish to report the threo selectivity is valid for various aldehydes,[4] and is characteristic of chromium in contrast to main group metals.



I (threo) II (erythro)

The reaction of trans-1-bromo-2-butene[5] with aldehydes in tetrahydrofuran (THF) resulted in the formation of threo homoallyl alcohols (I) with high degree of selectivity as summarized in Table 1 (run 1-10). The selectivity was almost independent of the chromium reagents, i.e. $CrCl_3$-1/2 $LiAlH_4$ or $CrCl_2$.[2] Compared with the reaction of crotylmetals derived from magnesium, zinc or cadmium,[6] the threo selectivity is in general extremely high for relatively unhindered aldehydes.[7] In N,N-dimethylformamide (DMF) the threo selectivity was reduced to 66-75% (run 11-13),[8] although the reaction took place more smoothly. The only exception of the threo selectivity was provided by a bulky aldehyde, 2,2-dimethylpropanal, which gave preferentially erythro alcohol (II) irrespective of the solvent (run 14, 15).[7]

With cis-1-bromo-2-butene (run 3),[5] again the threo alcohol was produced as the sole product. Thus, the stereochemical integrity was completely lost in contrast to the reaction of (Z)-2-butenylboron and -silicon derivatives.[9] Probably the isomerization occurred at the step of the formation of organochromium species.[10]

Table 1 Reaction of 1-Bromo-2-butene with Aldehydes Using Chromium(II) Reagents[a]

run	aldehyde	solvent	total yield (%)	threo :	erythro[b]
1	C_6H_5CHO	THF	96	100[c]	0[c]
2	C_6H_5CHO	THF	(100)	(90)[c]	(10)[c]
3	C_6H_5CHO	THF	87[d]	100	0
4	*n*-C_3H_7CHO	THF	59	93	7
5	*i*-C_3H_7CHO	THF	55	95	5
6	*i*-C_3H_7CHO	THF	(81)	(97)	(3)
7	*n*-$C_5H_{11}CHO$	THF	70	97	3
8	*n*-$C_5H_{11}CHO$	THF	(97)	(96)	(4)
9	*n*-$C_5H_{11}CHO$	THF[e]	88	94	6
10	*n*-$C_5H_{11}CHO$	THF[f]	88	95	5
11	C_6H_5CHO	DMF	92	75[c]	25[c]
12	*i*-C_3H_7CHO	DMF	78	66	34
13	*n*-$C_5H_{11}CHO$	DMF	77	68	32
14	*t*-C_4H_9CHO	DMF	63	37	63
15	*t*-C_4H_9CHO	THF	64	35	65
16	$CH_3CH{=}CHCHO$	THF	(73)	(83)[g]	(17)[g]
17	C_6H_5CHO	THF[h]	(83)	(83)[c]	(17)[c]

[a] Chromium(III) chloride (4 mol), lithium aluminum hydride (2 mol), 1-bromo-2-butene (2 mol) per 1 mol of an aldehyde were employed at room temperature (20 ± 3°C). The values in parentheses refer to the results obtained with the commercially available anhydrous chromium(II) chloride (4 mol).

[b] The stereochemistry of the products was determined by comparing the spectral properties and the GLC retention times with those of the authentic samples (see ref 6).

[c] Determined by ^1H-NMR (the absorption of the methine proton *H*-C-OH): threo, δ 4.26 (d, J = 6.8 Hz); erythro, δ 4.43 (d, J = 5.8 Hz).

[d] *cis*-1-Bromo-2-butene was used.

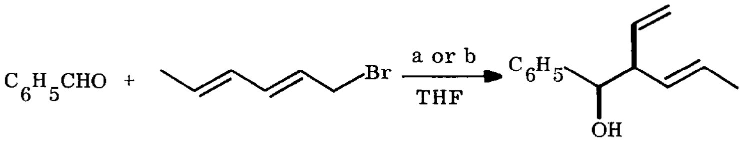
[e] At THF refluxing temperature.

[f] Triphenylphosphine (4 mol) was added.

[g] Determined by ^{13}C-NMR: threo (intensity)/erythro (intensity) δ 15.83 (94)/15.00 (20), 44.32 (99)/43.69 (20), 115.62 (99)/115.03 (19). Stereochemical assignment similar to β-hydroxycarboxylic acid: C. H. Heathcock, M. C. Pirrung, and J. E. Sohn, *J. Org. Chem.*, **44**, 4294 (1979).

[h] Pyridine (8 mol, 2 equivalents of chromium) was used.

The C-C bond formation with benzaldehyde and 1-bromo-2,4-hexadiene took place exclusively at the γ-position of the bromide[11] to give III. The stereochemistry of the major product was tentatively assigned to be the one depicted below in analogy to the results in Table 1.

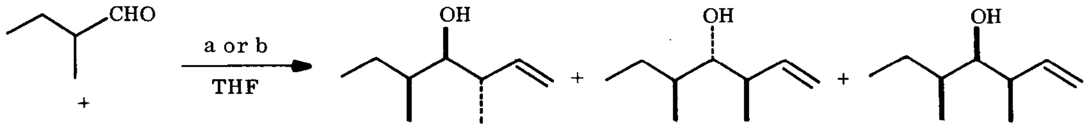


III

a: $CrCl_3$-1/2 $LiAlH_4$
82% yield (73:27)

b: $CrCl_2$, 95% yield, (74:26)

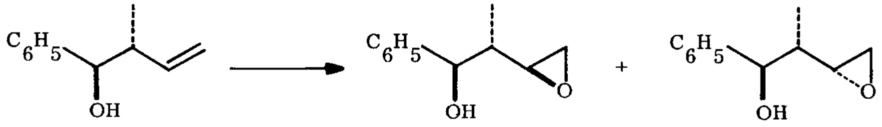
The threo selectivity of more than 93% (products IV and V) was observed in the reaction of 2-methylbutanal and 1-bromo-2-butene although α-erythro induction (IV/(IV + V)) was 69%.[3,9a]



IV V

a: $CrCl_3$-1/2 $LiAlH_4$, 78% yield	64%	29%	7%
b: $CrCl_2$, 90% yield	62%	31%	7%

The homoallyl alcohols thus obtained can be epoxidized to produce three contiguous asymmetric carbons.[13] For example, the Sharpless oxidation (t-BuOOH, VO(acac)$_2$)[14] of VI gave mainly the erythro epoxide VII[15] (52% yield, VII/VIII 76:24), whereas oxidation with aluminum t-butoxide and t-butylhydroperoxide[16] gave the threo epoxide VIII as the major product (51% yield, VII/VIII 18:82). m-Chloroperoxybenzoic acid turned out nonselective in this case to afford a 55:45 mixture of VII and VIII (69% yield).



VI VII VIII

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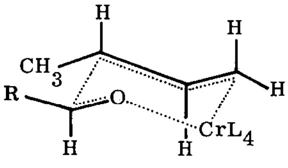
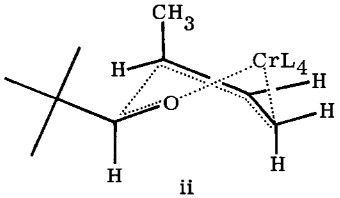
7. The selectivity may be explained in terms of a chair form transition state i wherein methyl-R interaction would be most reduced, whereas the erythro selective reaction of 2,2-dimethylpropanal may be understood by the anticipated severe interaction between t-butyl and methyl groups and accordingly by a preferred skew boat-like transition state ii.



i



ii

8. Chromium(III) ion has an octagonal configuration and consequently accepts six ligands (ref 12), which would have the effect on the selectivity. The low threo selectivity in DMF may be understood by the good solvating power of DMF compared with THF and by the increased bulkiness around the chromium metal to disfavor the transition state i. Based on this working hypothesis we added triphenylphosphine (4 mol) (see Table 1, run 10), the selectivity being somewhat decreased with increased yield. It is worth pointing out that the ligand such as pyridine which stabilizes the complex RCrCl$_2$(ligand)$_3$ (ref 12b) lowers the threo selectivity (see Table 1, run 17).
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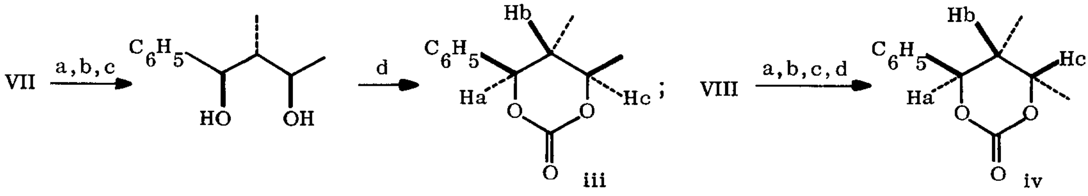
14. K. B. Sharpless and R. C. Michaelson, J. Am. Chem. Soc., 95, 6136 (1973)
15. The stereochemistry of VII was determined chemically by transforming the epoxide into the carbonate iii whose substituents should take all equatorial positions. The coupling constants are consistent to this conformation. On the other hand, VIII gave the carbonate iv. Examination of molecular models indicated this would take a skew boat form to reduce the methyl-methyl interaction, compatible with the ^{1}H-NMR data.



J_{ab} = 10.7 Hz, J_{bc} = 10.5 Hz J_{ab} = 7.8 Hz, J_{bc} = 3.4 Hz

a: EtOCH=CH$_2$, PyH·OTs, b: LiAlH$_4$, THF, reflux, c: EtOH, PyH·OTs, d: COCl$_2$, Et$_3$N

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