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1,4-Asymmetric Induction in the Nozaki-Hiyama Reaction

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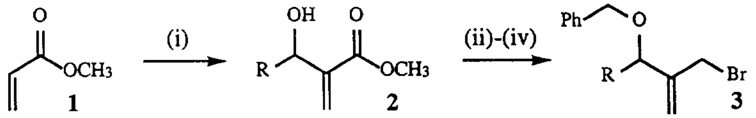
Abstract: *A series of allyl bromides 3a-c bearing a stereogenic carbon substituent at C-2 are synthesised in four steps from methyl acrylate. These are found to react with aldehydes, mediated by chromium(II) chloride, to furnish* syn-*4-alkoxyalkan-1-ols 4 in good to excellent diastereoselectivity.*

The chromium(II) chloride mediated coupling of an allyl bromide to an aldehyde was first reported separately by Nozaki and Heathcock.[1] One of the notable feature of the reaction is its excellent 1,2-*anti*-diastereoselection, regardless of the double bond geometry of the allyl bromide, and has been used to good effect in both an inter-[2] and intramolecular[3] fashion in natural product synthesis. In this communication, we wish to report the development of a 1,4-asymmetric induction technique utilising the Nozaki-Hiyama reaction. Whereas early work in the field of organometallic 1,4-asymmetric induction has been limited to allylsilane and allylstannane reagents,[4] and one specific example of a chromium(II) mediated coupling of a cyclic allyl iodide to an aldehyde,[5] the work described below illustrates a general method for the generation of chiral allyl bromides and their application to diastereoselective reactions.

For the synthesis of the allyl bromides **3 a-c** the Baylis-Hillman reaction was used[6]. Methyl acrylate (**1**) was left to stand with a series of aldehydes in the presence of 1,4-Diazabicyclo[2.2.2]octane (DABCO), to furnish hydroxyesters **2** in moderate yield. After benzyl protection using the method described by Bundle[7], the ester moiety was reduced using DIBAL-H, and the resulting allylic alcohols were converted into bromides **3** with *N*-bromosuccinimide and triphenylphosphine[8], (scheme 1).

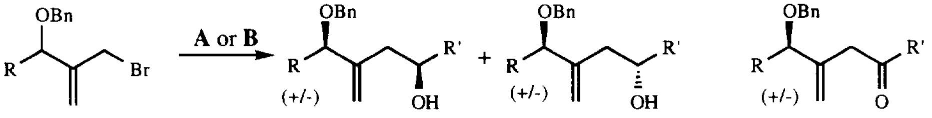


3a R=CH$_3$
3b R=Ph
3c R=iPr

(i) RCHO, DABCO (40-50%); (ii) (BnO)C(N=H)CCl$_3$, TfOH, cyclohexane-DCM (4:1) (85-98%); (iii) DIBAL-H, DCM, -78°C (87-97%); (iv) NBS, PPh$_3$, DCM, -18°C (65-71%)

Scheme 1

With the allyl bromide bearing a stereogenic carbon at C-2 in hand, the conditions for achieving maximal stereoinduction were investigated. When the reaction was performed in THF, a modest yield of adduct **4** was obtained, along with ketone **5** and benzyl alcohol; presumably the formation of the ketone occurs *via* an Oppenauer-type oxidation of the chromium alkoxide with benzaldehyde before quenching.



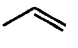
syn-**4** *anti*-**4** **5**

3a R = CH_3
3b R = Ph
3c R = *i*-Pr

cond. **A** : $CrCl_3$: $LiAlH_4$ (2:1), THF, then R'CHO, (**3**), 0°C
cond. **B** : $LiAlH_4$ (2:1), THF, then DMF, R'CHO, (**3**), -20°C

Scheme 2

Table 1. Yields and 1,4-Diastereoselectivity of the Hiyama Reaction

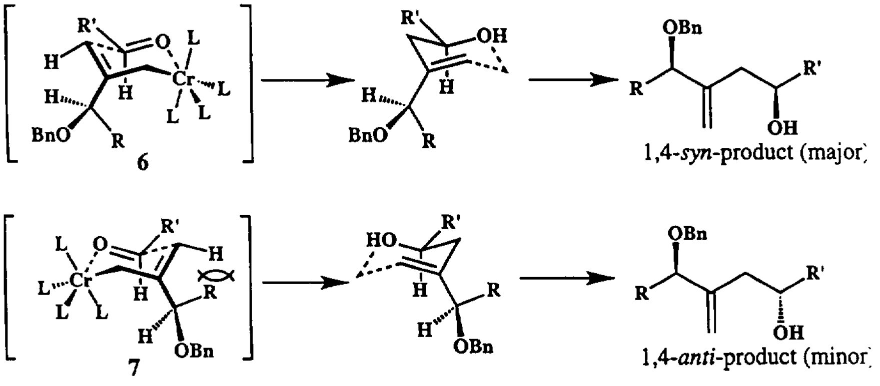
Entry	Allyl Bromide	R'	Cond.	Yield (%)	*syn*-**4** : *anti*-**4**
1	**3a**	Ph	A	39^b	64:36
2	**3a**	Ph	B	57	87:13
3	**3a**	Me	B	75	83:17
4	**3a**	Et	B	68	85:15
5	**3a**	^{i}Pr	B	71	81:19
6	**3a**	^{t}Bu	B	69	81:19
7	**3a**		B	26^c	85:15
8	**3a**	CO_2Et	B	complex	mixture
9	**3b**	Ph	B	71	91:9
10	**3c**	Ph	B	60	95:5

[a] determined by integration of C-1 methine proton nmr signal and by analogy with proven structure.

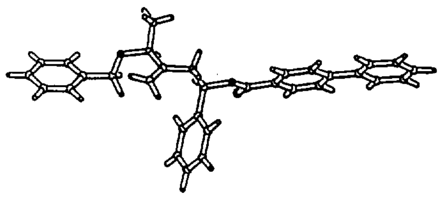
[b] 35% yield of ketone **5** obtained. [c] 47% yield of allyl chloride obtained.

Inspection of the n.m.r. spectra of homoallylic alcohols (**4**) revealed that significant stereoinduction had been achieved (table 1, entry 1). Upon changing the solvent to DMF, a good yield was obtained, the formation of ketone **5** was suppressed, and an improved level of stereoinduction was observed (scheme 2). The relative stereochemistry of the major product (syn-**4a**, R=CH_3, R'=Ph) was proved by X-ray structural analysis of the *p*-(4-phenyl)benzoate derivative 8[9]. The 1,4-asymmetric induction was further improved by reducing the reaction temperature to -20°C. Reactions performed at lower temperatures were found to be sluggish and gave no great improvement in diastereoselection (scheme 2). Further reactions were performed using alternate aldehydes and allyl bromides **3b** and **3c**, the results of which are presented in table 1. It must be noted that the reactions also returned *ca.* 10-25% of the bromide/chloride exchange product, and although allyl chlorides are known to react with aldehydes in DMF[1c], these did not participate under the conditions employed. In the case of the methyl allyl bromide (**3a**), both yield and the asymmetric induction in the reaction proved to be satisfactory. The more sterically demanding aldehydes (entries 5 and 6) caused a slight reduction in diastereoselectivity, but still gave ca. 70 % yield of adduct. When the methyl group is replaced by bulkier residues (entries 9 and 10), a significant improvement in the reaction selectivity occurs, providing excellent levels of *syn*-1,4-asymmetric induction, indicating that the spatial demands of the allyl bromide species dominate the stereochemical result. The reaction conditions proved to be too harsh for more unstable aldehydes (entries 7 and 8), this could well be due to the extended reaction time under the Lewis acidic conditions.

The preference of the reaction to afford 1,4-*syn*-products can be explained by the antiperiplanar approach of the aldehyde to the benzyloxy moiety, in a manner analagous to the Felkin-Anh model.[2b] A metallo-ene process then ensues, proceeding *via* a six-membered chair-like transition state, in which conformation (**6**) is preferred over **7**, as the 1,3-allylic strain in transition structure (**6**) will be considerably less than in **7**. This explanation is borne out by the observation that an increase in the size of residue (**3b** and **3c**) provides a significant improvement in the diastereoselectivity of the reaction (scheme 3).



Scheme 3



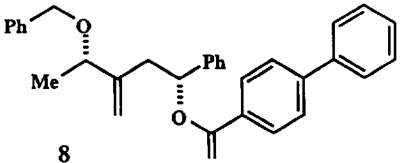


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Figure 1. Crystal structure of compound 8[9].

In conclusion, we have demonstrated that 1,4-asymmmetric induction can be achieved using chromium(II) methodology, and affords *syn*-4-benzyloxyalkan-1-ols in good chemical yield and good to excellent diastereoselectivity. Work is presently underway to determine the effect of altering the ethereal protecting group, and the application of this methodology to synthesis[10].

Acknowledgements

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References and Notes

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9. X-ray crystallographic data have been deposited with the Cambridge Cristallographic Data Centre. The data can be obtained, on request, from: The Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1 EZ, UK.
10. *General Procedure*:To a suspension of chromium(III) chloride (0.52 g, 3.3 mmol) in dry THF (13 ml) at 0°C, was added dropwise lithium aluminium hydride (1.63 ml, 1M in THF, 1.6 mmol) and the solution was stirred at RT for 30 min. THF was evaporated by gentle heating in a stream of argon and DMF (13 ml) was added. The black suspension was cooled to -20°C and benzaldehyde (0.18 ml, 1.8 mmol) added followed by **3c** (0.33 g, 1.2 mmol) in DMF (2 ml). The mixture was then stirred for 15 h at -20°C, then poured into a rapidly stirred suspension of ether (20ml), brine (20ml) and water (20ml) with a wash of ethyl acetate (20ml) and stirred rapidly for 48 h. The mixture was extracted with ether (x3), washed with brine and dried. Chromatography on silica gel (*n*-hexane-ether, 10:1) as eluent, afforded (1RS, 4SR)-4-benzyloxy-5-methyl-3-methylidene-1-phenyl-1-hexanol (*syn*-**4c**) (0.22 g, 60%).^{1}**H-NMR** ($CDCl_3$; 250 MHz): δ = 0.79 (3H, d, *J*6.8), 1.01 (3H, d, *J*6.5), 1.90 (1H, m), 2.44 (1H, dd, *J*15.4, 8.4), 2.57 (1H, dd, *J*15.4, 4.3), 3.31 (1H, d, *J*8.8), 4.20 and 4.48 (each 1H, d, *J*11.8), 4.97 (1H, dd, *J*8.4, 4.3), 5.08 (1H, d, *J*1.4), 5.14 (1H, d, *J*1.4) , 7.31 (10H, m).

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