Asymmetric Induction in the Darzens Reaction by using an η^6-Cr(CO)$_3$ complexed Arene as Chiral Auxiliary

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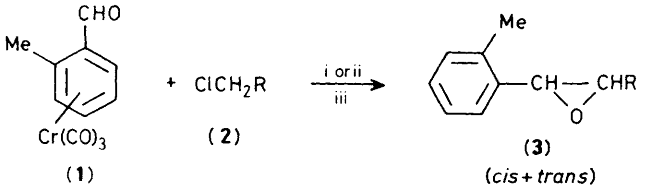
Enantioselective Darzens condensation has been achieved from optically active 2-methylbenzaldehyde(tricarbonyl)chromium; enantiomeric excesses are in the range 40—88%.

Optically active oxiranes are interesting intermediates for the synthesis of biologically active compounds; there are several methods for their preparation,[1] but one of the most widely used for epoxides carrying electron withdrawing substituents is the Darzens reaction. There are few literature examples of asymmetric Darzens condensation and, in most cases, the enantiomeric excesses (e.e.) are low.[2,3] Epoxy-ketones, however, are obtained in up to 63% e.e. when aromatic aldehydes are treated with phenacyl halides in an aqueous medium and in the presence of a catalytic quantity of bovine serum albumin.[4] More recently, enantiomerically pure *cis*-α,β-epoxy-carboxylates were prepared using a modified Darzens procedure: aldol condensation of various aldehydes with chiral halogenoimides.[5]

There has been a notable increase recently[6—8] in the use of *ortho*- and *meta*-disubstituted η^6-Cr(CO)$_3$ complexed arenes as chiral auxiliaries in asymmetric synthesis. The use of such chiral auxiliaries often leads to a high degree of diastereo- and enantio-selectivity; the fact that Cr(CO)$_3$ complexed 2-methylbenzaldehyde (**1**) can be prepared in an enantiomerically pure form[9,10] prompted us to employ it in asymmetric Darzens condensations (Scheme 1).



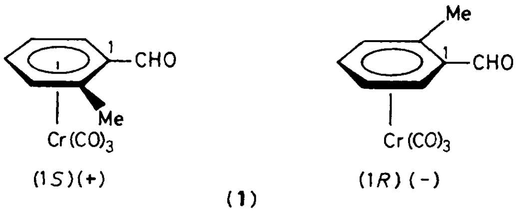
a: R = CN
b: R = CO_2Bu^t
c: R = COPh

Scheme 1. *Reagents:* i, KOH, TOAB, C_6H_6; ii, Bu^tOK–Bu^tOH; iii, 30% H_2O_2, TOAB, CH_2Cl_2 (all at room temperature).

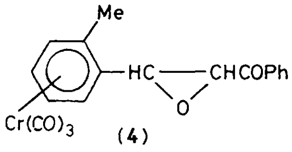
Table 1. Darzens reactions of optically active $Cr(CO)_3$-complexed 2-methylbenzaldehyde (**1**) and uncomplexed 2-methylbenzaldehyde.

Oxirane[a]	Conditions	% Yield[b]	*cis* : *trans*[b]	E.e. (±3%) *cis*	E.e. (±3%) *trans*
cis- + *trans*-(**3a**)	A	70 (80)	63 : 37 (58 : 42)	40	40
cis- + *trans*-(**3a**)	B	70 (75)	69 : 31 (46 : 54)	59	56
cis- + *trans*-(**3b**)	A	65 (75)	77 : 23 (80 : 20)	43	40
cis- + *trans*-(**3b**)	B	70 (75)	72 : 28 (67 : 33)	47	40
cis-(**3c**)	−78 °C, NaH, THF, HMPA	61	0 : 100	—	88
cis-(**3c**)	A	66 (58)	0 : 100 (0 : 100)	—	86
cis-(**3c**)	B	75 (85)	0 : 100 (0 : 100)	—	80

[a] All oxiranes gave analytical and spectroscopic data in agreement with their assigned structures. ^{1}H N.m.r. (90 MHz) δ ($CDCl_3$, Me_4Si): *cis*-(**3a**): 2.4 (s, 3H, CH_3), 3.77 (d, 1H, *J* 3.6 Hz), 4.2 (d, 1H, *J* 3.6 Hz), and 7.05—7.4 (m, 4H, ArH); *trans*-(**3a**): 2.45 (s, 3H, CH_3), 3.3 (d, 1H, *J* 1.95 Hz), 4.4 (d, 1H, *J* 1.95 Hz), and 7.05—7.4 (m, 4H, ArH); *cis*-(**3b**): 2.32 (s, 3H, CH_3), 3.75 (d, 1H, *J* 4.8 Hz), 4.19 (d, 1H, *J* 4.8 Hz), and 7.0—7.5 (m, 4H, ArH); *trans*-(**3b**): 2.38 (s, 3H, CH_3), 3.32 (d, 1H, *J* 1.8 Hz), 4.15 (d, 1H, *J* 1.8 Hz), and 7.0—7.5 (m, 4H, ArH); *trans*-(**3c**): (CCl_4) 2.35 (s, 3H, CH_3), 3.9 (d, 1H, *J* 1.85 Hz), 4.1 (d, 1H, *J* 1.85 Hz), and 6.8—8.3 (m, 9H, ArH). [b] Yields and *cis* : *trans* ratio of the reactions performed on uncomplexed 2-methylbenzaldehyde in parentheses.



(**1**)



(**4**)

The reactions were first performed at −78 °C; NaH (2.3 mmol) was added to a stirred solution of (−)-(1*R*)-2-methylbenzaldehyde(tricarbonyl)chromium (**1**) (2.0 mmol), and the chloro-derivatives (**2a**—**c**) (2.0 mmol) in anhydrous tetrahydrofuran (THF) (20 ml) and hexamethylphosphoramide (HMPA) (2 ml). The reaction progress was monitored by t.l.c. (eluant: Et_2O–light petroleum, 1 : 1). Compounds (**2a**) and (**2b**) did not react at all. In the case of (**2c**), after 10 h the mixture was poured into 50 ml of water, extracted with ether, and the organic layer dried over Na_2SO_4. Evaporation gave, after chromatography on a silica gel column (eluant: Et_2O–light petroleum, 1 : 1), the optically active ($Cr(CO)_3$ complexed oxirane derivative (**4**)† as the *threo* diastereoisomer‡ in 61% yield. This diastereoselectivity corresponds with the reported behaviour of phenacyl chloride in the Darzens reaction.[4] The decomplexed epoxide (**3c**), in the presence of $Eu(tfc)_3$ {tfc = 3-[trifluoromethylhydroxymethylene]-(+)-camphorato} as the chiral shift reagent (see Table 1), was shown to have e.e. 88%.

As (**2a**) and (**2b**) showed no reactivity at −78 °C we varied the temperature and finally repeated all reactions at room temperature. Two different experimental conditions were selected: (i) solid–liquid phase transfer catalysis (PTC) (experiment A); (ii) homogeneous Bu^tOH solution (experiment B).

Experiment A: the appropriate (**2**) (1.7 mmol), tetraoctylammonium bromide (TOAB) (0.16 mmol), and powdered KOH (3.2 mmol) were added to a vigorously stirred solution of optically active (−)-(1*R*)- or (+)-(1*S*)-(**1**) (1.6 mmol) in benzene (40 ml). The reaction progress was monitored by t.l.c. (eluant: Et_2O–light petroleum, 1 : 1); when (**1**) had disappeared, the solvent was evaporated off under reduced pressure, and the residue taken up with CH_2Cl_2 and filtered over Celite. Decomplexation was performed at room temperature using TOAB (0.1 mmol) as phase transfer catalyst and by treating the CH_2Cl_2 solution with an excess of 30% H_2O_2 (3 ml) for 5 h.

Experiment B: a solution of Bu^tOK (1.7 mmol) in Bu^tOH (30 ml) was added in drops to a stirred solution of (−)-(1*R*)- or (+)-(1*S*)-(**1**) (1.6 mmol) and the appropriate (**2**) (1.7 mmol) in Bu^tOH (10 ml); the temperature was kept under 27 °C. At completion (t.l.c.) the mixture was diluted with water (40 ml), extracted with CH_2Cl_2 (4 × 20 ml), and decomplexed at room temperature as before.

Yields, *cis* : *trans* ratios, e.e. values, and ^{1}H n.m.r. data of the oxiranes (**3a**—**c**) obtained are reported in Table 1; all values represent an average from three different reactions carried out under the same conditions. Uncomplexed 2-methylbenzaldehyde was analogously treated with (**2a**—**c**) giving (**3a**—**c**) with a *cis* : *trans*-isomer ratio and yields comparable to those obtained from the complexed aldehyde (**1**). The e.e. was determined directly from the diastereoisomeric mixture: $Eu(hfc)_3$ {hfc = 3-[heptafluoropropylhydroxymethylene]-(+)-camphorato} in $CDCl_3$ solution was used for (**3a**,**b**) and $Eu(tfc)_3$ in CCl_4 solution for (**3c**).

Both the enantioselectivity and the diastereoselectivity increased on passing from (**3a**) to (**3c**). In the latter case the reaction is 100% diastereoselective and compound (**3c**) is obtained and isolated as a pure *trans*-isomer in up to 80% e.e. In any case, even working at room temperature, e.e. values were never lower than 40%.

The dependence of the optical purity of the oxiranes (**3a**—**c**) on the conditions (experiment A or B) is relevant only in the

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† ^{1}H N.m.r. ($CDCl_3$, Me_4Si) δ 2.25 (s, 3H, CH_3), 4.0 [d, 1H, *J* 1.5 Hz, *C*HArCr(CO)$_3$], 4.1 (d, 1H, *J* 1.5 Hz, CHCOPh), 4.85—5.8 [m, 4H, ArCr(CO)$_3$], and 7.1—8.2 (m, 5H, PhCO).

‡ The oxirane (**3c**) obtained by decomplexation of (**4**) was identical to an authentic sample prepared, following the literature procedure,[11] from the corresponding *trans*-chalcone by epoxidation with H_2O_2 in alkaline medium.

case of (**3a**) where the degree of asymmetric induction in homogeneous medium is higher than in PTC.

It is noteworthy that no epimerization occurs on treating the crude optically active complexed oxiranes with 40% NaOD in $CDCl_3$; this was indicated by the absence of H/D exchange. No change occurs in the diastereoisomeric ratio during the decomplexation procedure.

We thank CNR, Rome, for financial support.

Received, 15th December 1986; Com. 1785

References

1 A. S. Rao, S. K. Paknikaz, and J. G. Kirtane, *Tetrahedron*, 1983, **39**, 2323, and references cited therein.
2 S. Colonna, R. Fornasier, and V. Pfeiffer, *J. Chem. Soc., Perkin Trans. 1*, 1978, 8.
3 J. C. Hummelen and H. Wynberg, *Tetrahedron Lett.*, 1978, **12**, 1089.
4 R. Annunziata, S. Banfi, and S. Colonna, *Tetrahedron Lett.*, 1985, **25**, 2471.
5 A. Abdel-Magid, L. N. Pridgen, D. S. Eggleston, and I. Lantos, *J. Am. Chem. Soc.*, 1986, **108**, 4595.
6 A. Solladié-Cavallo and J. Suffert, *Tetrahedron Lett.*, 1985, **26**, 429.
7 A. Solladié-Cavallo and J. Suffert, *Tetrahedron Lett.*, 1984, **19**, 1987, and references cited therein.
8 G. Jaouen, in 'Transition Metal Organometallics in Organic Synthesis,' ed. H. Alper, Academic Press, New York, 1978, vol. 33-II, pp. 65–120.
9 A. Solladié-Cavallo, G. Solladié, and E. Tsamo, *J. Org. Chem.*, 1979, **44**, 4189.
10 A. Solladié-Cavallo and J. Suffert, *Magn. Reson. Chem.*, 1985, **23**, 739.
11 E. Weitz and A. Scheffer, *Ber.*, 1921, **54**, 2347.