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Asymmetric Induction in The Nucleophile Addition to η^6-Arene-Tricarbonyl-Chromium(0) Complexes

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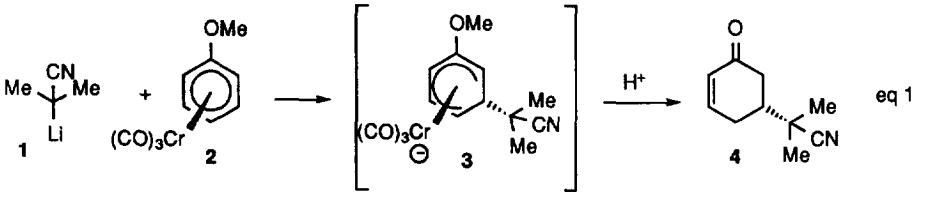
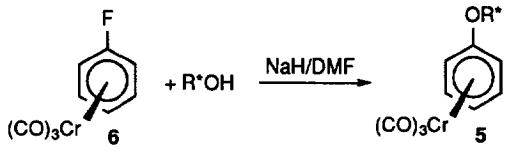
Abstract: The addition of 2-lithio-2-methylpropionitrile (**1**) to chirally modified η^6-arene-tricarbonylchromium complexes (**5**) leads to the formation of 2-(cyclohex-2-en-1-on-5-yl)-2-methylpropionitrile (**4**) in good yields and, under thermodynamically controlled conditions, with up to 48% ee.

As reported earlier,[1] the addition of nucleophiles such as 2-lithio-2-methylpropionitrile (**1**) to η^6-anisole-tricarbonylchromium (**2**) proceeds with high regioselectivity (*meta* attack) to form an anionic intermediate (rac-**3**), which, on quenching with trifluoroacetic acid and hydrolysis of the initially formed mixture of dienolethers, is converted into the substituted cyclohexenone derivative (rac-**4**) in moderate to high overall yield (eq 1). The product is formed as a racemic mixture because the (achiral) nucleophile must attack the enantiotopic *meta* positions of **2** with equal probability.

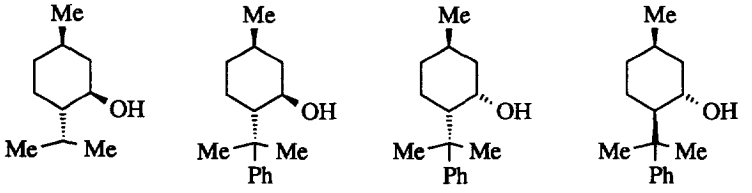


If an element of asymmetry is built into the metal ligand system, enantioselectivity in the formation of **4** may result. The ideal asymmetric element will optimize effectiveness (inducing high ee) with operational efficiency (in introduction and recycling of the chiral auxiliary). With little detailed knowledge of the transition state for nucelophile addition, it is not possible to predict with confidence the influence of an asymmetric ligand or asymmetric substituent on the stereoselectivity of addition. From an operational standpoint, an attractive process with arene-metal systems is the positioning on the arene of a heteroatom substituent bearing an asymmetric group via metal-promoted S_NAr substitution for halide.[2] This concept has been used to provide asymmetric precursors for nucleophilic addition to cationic arene-$Mn(CO)_3$ complexes; unfortunately, while the % ee can be as high as 90% in forming the intermediate cyclohexadienyl Mn complexes (analogs of **3**), the intermediates are not easy to convert to simple organic products (analogs of **4**).[3] Compounds of type **5**, bearing a chiral alkoxy (OR*) substituent, should lead to **4** or ent-**4** with asymmetric induction, because one of the diastereotopic *meta* positions of **5** should now be attacked preferentially, and stereospecifically from the exo face. There is no basis at present for predicting which isomer will be preferred nor the degree of selectivity. We undertook to probe the sensitivity to the asymmetric environment provided by OR* by evaluating experimentally simple processes involving **5**. Complexes of type **5** were prepared in one step from the fluorobenzene complex **6**[4] and the respective homochiral alcohols (R*OH = **7-10**; eq 2). As R*OH, (-)-menthol (**7**), (-)-8-phenylmenthol (**8**),[5] (+)-8-phenylneomenthol (**9**),[6] and (+)-8-phenylisomenthol (**10**)[7] were employed (Table 1).



a : R*OH = **7**
b : R*OH = **8**
c : R*OH = **9**
d : R*OH = **10**

eq 2



7 **8** **9** **10**

Table 1: Preparation of the chiral complexes **5** according to Eq 2.[8,9]

*R*OH*	*product*	*yield*	*mp*	*$[\alpha]_D^{20}$ in ethanol*
7	**5a**	81 %	124- 25 °C	- 67.7 ° (c = 0.53)
8	**5b**	68 %	117-118 °C	+56.2 ° (c = 1.13)
9	**5c**	71 %	(oil)	- 24.5 ° (c = 0.74)
10	**5d**	75 %	115 - 116 °C	- 36.9 ° (c = 0.48)

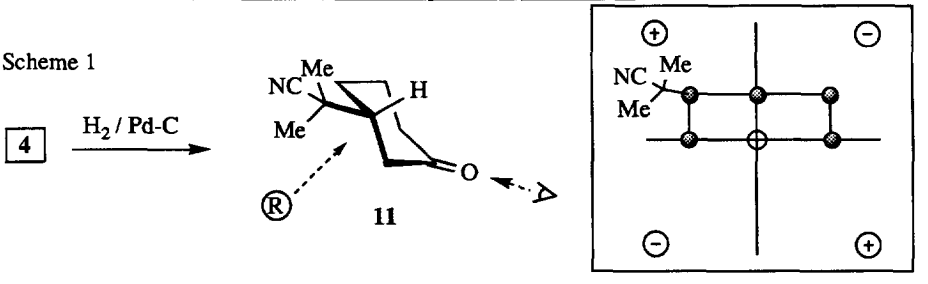
The nucleophile additions to the complexes **5** were carried out on a 0.75 to 1.0 mmol scale by adding the complex **5** at -78 °C to a THF solution of anion **1** (2 mol-eq, prepared from isobutyronitrile and LDA) followed by stirring the mixture for a certain time and temperature, as specified in Table 2. Analysis was performed as follows: At -78 °C, 0.25 mL of trifluoroacetic acid (TFA) was added to the reaction mixture, which was then diluted with ether, and washed sequentially with cold aqueous ammonium hydroxide and with brine. After evaporation of the solvents, the residue (mixture of enolethers) was treated with aqueous HCl in THF at 70 °C, until TLC indicated complete conversion (ca. 1.5 h). Partition between brine and hexane/ether (5:1), drying and concentration of the organic layer, and flash chromatography (hexane/EtOAc, 1.5:1) of the residue gave a mixture of **4**/ent-**4** as a colorless solid separate from varying amounts (typically 60 to 80 %) of the respective recovered chiral auxiliary alcohol (**7**-**10**).

The absolute configuration of **4** was assigned in the following way: A sample of (-)-**4** (18% ee) was hydrogenated (Scheme 1) and the resulting ß-substituted cyclohexanone (-)-**11**[11] was analyzed by CD-spectroscopy. A positive Cotton-effect at the ketone ($n \rightarrow \pi^*$) band (λ = 283 nm) and application of the octant rule[12] established that the major isomer is the (R)-isomer of **11** (Scheme 1). Therefore, compound **4** with a negative molecular rotation must also be (R)-configured.

Table 2: Preparation of 4/ent-4 by addition of **1** to complexes **5** followed by TFA quench and hydrolysis.[10]

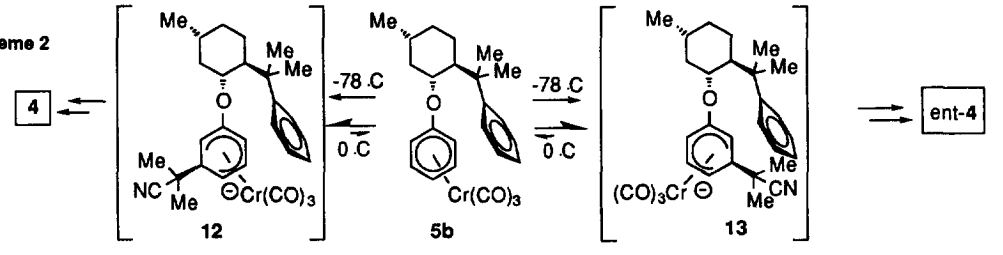
entry	*complex*	*temp; time*	*yield*	$[\alpha]_D$	*ee.*	*major enantiomer*
1	**5a**	-78 °C; 3 h	80 %	-10.6 °	15 %	**4**
2	**5a**	0 °C; 2.5 h	65 %	-16.1 °	22 %	**4**
3	**5b**	-78 °C; 3 h	76 %	-10.3 °	14 %	**4**
4	**5b**	0 °C; 3.5 h	73 %	-35.8 °	48 %	**4**
5	**5b**	0-10 °C 10 h	70 %	-29.4 °	42 %	**4**
6	**5c**	-78 °C; 3.5 h	62 %	-6.1 °	10 %	**4**
7	**5c**	0 °C; 3.5 h	63 %	+9.0 °	13 %	ent-**4**
8	**5d**	-78 °C; 4 h	45 %	+0.8 °	<2 %	ent-**4**
9	**5d**	0 °C; 3.5 h	76 %	+20.9 °	32 %	ent-**4**

Scheme 1



The results of the various experiments, summarized in Table 2, clearly indicate that the reactions worked well at various temperatures, providing 4/ent-4 in reliable chemical yields. Remarkably, the enantiomeric excess of the product was always different (higher) when the reactions were run at 0 °C instead of -78 °C. Even the absolute configuration of the major product enantiomer was found to be dependent on the reaction temperature in one case (**5c**). This behavior may be explained in the following way: at low temperatures (-78 °C), the nucleophile attack is irreversible (kinetically controlled) and occurs (slightly) preferentially at the less hindered meta position to give, in the case of **5b**, the diastereomeric intermediates **12** and **13** (Scheme 3) in a ratio of about 1.3:1 (14 % de). On warming the mixture to 0°C, the reverse reaction operates at a reasonable rate and the reaction becomes thermodynamically controlled.[14] The ratio of the intermediates changes; in the case of **5b**, to ca. 3:1 (48 % de).

Scheme 2



The enantiomeric excesses achieved so far (up to 48 % ee) are only moderate by modern standards. However, the ready accessibility of the chiral complexes **5**, the easy recycling of the chiral auxiliary, and the potential preparative value of **4** (or related compounds) suggest significant value of the methodology.[14]

References and Notes

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2. For a review of this general process, see: M. F. Semmelhack in "Comprehensive Organic Synthesis," B. M. Trost and I. Fleming, eds.; Vol 4, Pergamon Press, Oxford, 1992, p 521ff. See also reference 1d.

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4. Complex **6** (mp 122 - 123 °C) was prepared in 91 % yield according to the procedure of Mahaffy, C. A. L.; Pauson, P. L.,*Inorg. Synth.*, **1979**, *19*, 154.

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8. The reactions were carried out by adding **6** (1 mol-eq) to a solution of R*OH (1 mol-eq) and NaH (1.5 mol-eq) in DMF and stirring the mixture at 23 °C under argon in the dark for 12 to 24 h. Yields refer to analytically pure products after flash-chromatography (hexane/CH_2Cl_2 = 1.5:1 and/or hexane/EtOAc = 6:1). Melting points after recrystallization from ether/pentane (except **5c**). Data for compound **5b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ0.85-1.77 (m,6H), 0.96 (d,1H, J=6.5), 1.27 (s, 3H), 1.30 (s,3H), 2.04 (dt,1H, J_d=3.3, J_t=11), 2.23 (m,1H), 3.90 (dt,1H, J_d=4.2, J_t=10.4), 4.56 (dd,1H, J=2.0, J=6.8), 4.83 (t,1H, J=6.0), 4.96 (dd,1H, J=2.1, J=6.8), 5.45 (m,2H), 7.14-7.41 (m,5H). ^{13}C NMR (acetone-d_6): δ21.6(q), 26.4(t), 26.7(q), 26.8(q), 30.9(d), 34.4(t), 39.8(s), 40.2(t), 51.6(d), 78.2(d), 79.7(d), 82.3(d), 86.9(d), 95.9(d), 96.5(d), 125.1(d), 125.6(d), 128.0(d), 142.4(s), 151.2(s), 234.3(s) ppm. FT-IR ($CHCl_3$): 1964(s), 1886(s), 1528(m), 1462(m) cm^{-1}. MS: m/e 444.0 (M+). *Anal.* calc.: C 67.55 %, H 6.35 %; found: C 67.61 %, H 6.43 %.

9. All products were fully characterized by IR, ^{1}H NMR, ^{13}C NMR, MS and elemental analysis.

10. The enantiomeric excess (ee) of the product (**4**/ent-**4**) was in each case determined by ^{1}H NMR spectroscopy employing the chiral shift reagent Yb(Hfc)$_3$ in $CDCl_3$.

11. Data of compound **11**: Mol. rotations (at 20 °C, in $CHCl_3$, c=1.278): $[\alpha]_{589}$= -1.3°; $[\alpha]_{578}$= +0.5°; $[\alpha]_{365}$= +26.0°. ^{1}H NMR (300 MHz, $CDCl_3$): δ1.30 (s,3H), 1.36 (s,3H), 1.42-1.78 (m,3H), 2.07-2.43 (m,5H), 2.53 (dm, 1H). After addition of Yb(hfc)$_3$ (8 mg added to 10 mg of the sample in 0.4 mL $CDCl_3$) the s at 1.30 split into two s with relative integrations of 59:41 which corresponds to an ee of 18 %. ^{13}C-NMR ($CDCl_3$): 24.8(t), 25.1(q), 25.6(q), 27.3(t), 36.8(s), 41.4(t), 43.9(t), 47.1(d), 124.1(s), 210.2(s). FT IR ($CHCl_3$): 2234(m), 1709(s) cm^{-1}. MS: m/e 165.0(M+). *Anal.* calc.: C 72.69 % , H 9.15 %; found: C 72.42 %, H 9.16 %.

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13. We thank Prof. Nakanishi and Dr. Chang Mayland from Columbia University for recording the CD-spectrum of compound **11**.

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