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Catalytic enantioselective cycloadditions: a readily available Diels–Alder catalyst

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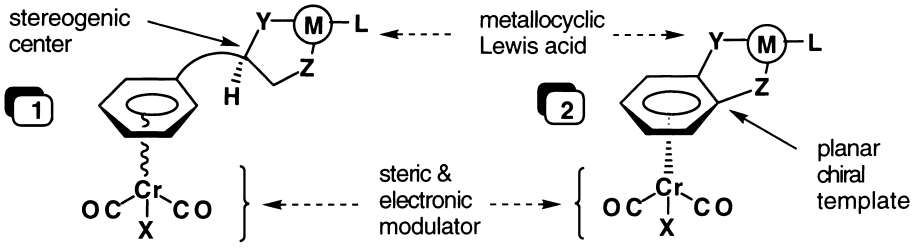
Abstract

A highly selective Diels–Alder catalyst has been prepared from a commercially available tetrahydronaphthalene diol. Stereocontrol is enhanced by introduction of a planar chiral arene chromium tricarbonyl group.

Following on from their extensive application in asymmetric synthesis,[1] the use of arene chromium carbonyl complexes as asymmetric catalysts is now becoming commonplace.[2] We, and others, have demonstrated that the tricarbonyl chromium group is a powerful stereodirective element in both chiral catalysts and auxiliaries,[3,4] and that electronic control is afforded by mixed-ligand arene chromium carbonyl systems, ranging from inductive effects on ring substituents[5] to modulation of arene facial π donor ability.[6] Combined, these effects can serve as powerful control elements in catalyst design, either by amplifying asymmetric induction of existing arene-based catalysts **1** or by introduction of a planar chirality **2**.



Based on encouraging results in cycloaddition reactions,[6] we sought to develop an efficient and readily available intermolecular Diels–Alder catalyst, incorporating the above design features.

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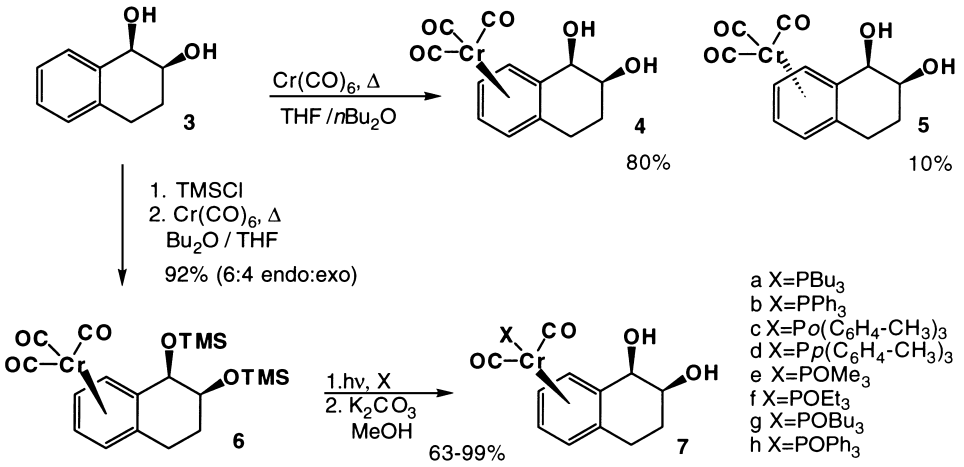
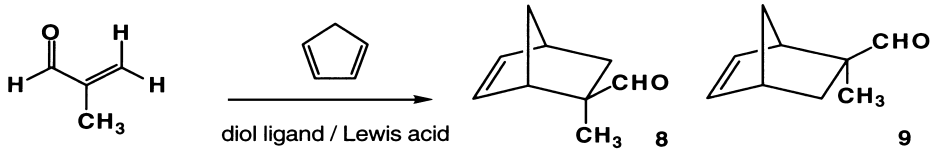
Specifically, we sought a commercially available building block which: (i) offered the potential for the formation of a metallocyle; and (ii) could be directly converted to a planar chiral arene complex. (1*R*,2*S*)-1,2,3,4-Tetrahydro-1,2-naphthalenediol **3** was selected, and converted directly to **4** in high yield by thermolysis with hexacarbonylchromium (Scheme 1). As is typical in such reactions, the *endo* complex predominates, giving an 8:1 mixture of **4**:**5** when a THF/*n*-butyl ether solvent mixture is used for complexation.[7] Alternatively, protection of the diol, then complexation, gave a mixture of **6** and its *exo*-isomer, readily separable when using SGC. Stereochemical assignment of **6** was confirmed by X-ray crystallography,[8] and this key intermediate allowed ligand substitution to be performed, giving a range of mixed-ligand complexes **7** on deprotection.



Scheme 1. Preparation of mixed ligand naphthalene diol complexes

The ligands were then exposed to a variety of Lewis acids, and the resulting metallocycles/chelates examined in the catalytic enantioselective cycloaddition of 2-methacrolein with cyclopentadiene, using catalysts derived from **3** as controls (Scheme 2). In all cases examined, *exo*-*R* cycloadduct **8** was formed in preference to *S*-**9**.[9]



Scheme 2. Metallodioxolane catalyzed [4+2] cycloadditions

The uncomplexed diol **3** alone offered moderate to good enantioselectivity, performing better with aluminum-derived metallocycles (Table 1, entries 1–4). Enhancement using the corresponding arene complexes was indeed possible, but restricted to *endo* ligand **4** (entries 5–7). While a slight decrease in selectivity was observed when using 10 mol% of a catalyst, no substantial increases were observed when using stoichiometric amounts; however, at lower temperatures the selectivity was increased marginally (entries 8–11). The diol ligand **4** could be recovered intact following hydrolytic workup, making this an attractive candidate for use in asymmetric syntheses. We anticipated that modification of the steric parameters around the ligand tripod of **4** would

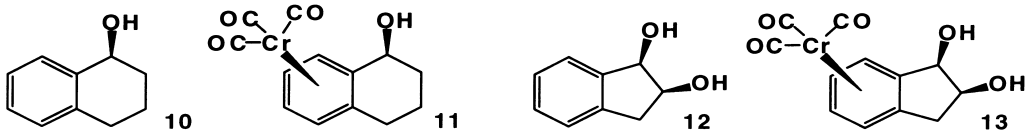
Table 1
Enantioselective cycloaddition of 2-methacrolein using diol catalysts[a]

Entry	ligand	mol%	Lewis acid	Temp	% 8[b]	exo:endo[c]	%e.e.[d]
1	**3**	20	BH_3.THF	-78°C	84	93:7	23
2	**3**	20	$BHBr_2.Me_2S$	-78°C	72	88:12	19
3	**3**	20	$EtAlCl_2$	-78°C	84	97:3	48
4	**3**	20	Et_2AlCl	-78°C	90	89:11	54
5	**4**	20	$EtAlCl_2$	-78°C	89	95:5	79
6	**4**	20	Et_2AlCl	-78°C	83	96:4	90
7	**5**	20	Et_2AlCl	-78°C	79	83:17	25
8	**4**	10	Et_2AlCl	-78°C	82	98:2	84
9	**4**	10	$EtAlCl_2$	-78°C	80	89:11	72
10	**4**	100	Et_2AlCl	-78°C	87	98:2	91
11	**4**	20	Et_2AlCl	-95°C	**81**	**98:2**	**95**
12	**7a**	20	Et_2AlCl	-78°C	85	93:7	66
13	**7a**	20	$EtAlCl_2$	-78°C	77	93:7	49
14	**7b**	20	Et_2AlCl	-78°C	32	80:20	56
15	**7c**	20	Et_2AlCl	-78°C	99	91:9	55
16	**7d**	20	Et_2AlCl	-78°C	88	89:11	62
17	**7e**	20	Et_2AlCl	-78°C	99	95:5	60
18	**7f**	20	Et_2AlCl	-78°C	99	97:3	78
19	**7g**	20	Et_2AlCl	-78°C	59	72:28	78
20	**7h**	20	Et_2AlCl	-78°C	86	95:5	86
21	**7h**	20	$EtAlCl_2$	-78°C	92	95:5	71
22	**10**	20	Et_2AlCl	-78°C	82	86:14	29
23	**11**	20	Et_2AlCl	-78°C	89	92:8	43
24	**12**[e]	20	Et_2AlCl	-78°C	62	88:12	29
25	**13**[e]	20	Et_2AlCl	-78°C	70	92:8	18
26	**13**[f]	20	Et_2AlCl	-78°C	89	95:5	14
27	**12**[e]	20	$EtAlCl_2$	-78°C	66	97:3	22
28	**13**[e]	20	$EtAlCl_2$	-78°C	81	97:3	28
29	**12**[e]	20	$BH_2Br.Me_2S$	-78°C	89	95:5	13
30	**13**[e]	20	$BH_2Br.Me_2S$	-78°C	58	99:1	62

(a) Ligand and Lewis acid equilibrated at 25°C/1h then cooled to –78° for addition of substrates. All reactions employed 0.5 mmol substrate in CH_2Cl_2; (b) isolated yields following SGC; (c) determined by ^1H NMR of crude isolates; (d) determined by chiral shift analysis using $Eu(hfc)_3$; (e) e.e. of diol ligand was 47%; (f) e.e. of diol ligand was 21%.

provide further increases in selectivity. Surveying a panel of eight different mixed-ligand derivatives **7a**–**h** failed to yield any improvement over the 'parent' tricarbonyl chromium complex (entries 12–21). The reasons for this could be several fold, including competing interactions of the Lewis acidic aluminum center with the phosphine and phosphite ligands. However, in contrast to the tricarbonyl complexes, in situ decomplexation of these mixed-ligand systems proved problematic, and, given the inferior performance of ligand **3**, the figures reported presumably reflect this process. The superior performance of catalysts derived from diethyl aluminum chloride suggests the involvement of a five-membered chloroaluminum metallocyclic Lewis acid. Indeed, in all the reactions studied, the aluminum species and diol were pre-equilibrated for 1 h before addition of the substrates. Reduction of this time led to a precipitous drop in product ee, since free aluminum Lewis acid is available to catalyze the reaction. To scrutinize this assumption further, analogous catalysts derived from (*S*)-tetralols **10** and **11** were prepared, and provided, as expected, greatly inferior stereocontrol. The (1*R*,2*S*) indanediol ligand **12** was then synthesized, and catalysts derived from **12** and **13** prepared. Unfortunately, despite numerous refinements, the direct route to **12** (asymmetric dihydroxylation of indene) provided diol ligand in $< 50\%$ ee.[10] Nevertheless,

preliminary analysis suggests that appreciable selectivity is attainable from this ligand family, an aluminum metallocycle derived from **13** giving a product ee in excess of 60% (entry 30). Chemoenzymatic routes to enantiomerically pure **12** together with various resolution protocols are thus currently under study.



Our working hypothesis for the transition state assembly involves preferential substrate [enal] coordination *exo* to the metallocycle, influenced heavily by the η^6-arene complex. We speculate that additional interactions of the aluminum species with the metal carbonyl tripod may explain the anomalously high levels of asymmetric induction attained using **4**.[11] Efforts to address this issue with the preparation of single crystals suitable for X-ray diffraction are underway.

In summary, a planar chiral asymmetric Diels–Alder catalyst has been developed. The best ligand **4** can be prepared in one step from a commercially available diol, making the catalyst a viable and readily available entity. The applicability of this system in the catalysis of a variety of cycloadditions will be reported in due course.

Preparation of **4**: (1*R*,2*S*)-1,2,3,4-tetrahydro-1,2-naphthalenediol (0.41 g, 2.5 mmol) and hexacarbonylchromium (1.1 g, 5 mmol) were dissolved in a 6:1 mixture of di-*n*-butyl ether and THF (70 ml), and the solution degassed (3×) then refluxed (N_2 atmosphere) for 24 h. On cooling to ambient temperature, the mixture was filtered through a plug of silica gel, concentrated in vacuo, and the resulting oil purified using SGC (6:4 through 9:1 EtOAc:hexanes as eluent), to give **4** (0.60 g, 92%) as a yellow solid, m.p. 104–106°C (dec.). ^{13}C (75 MHz, $CDCl_3$) 233.2, 112.6, 109.4, 95.9, 95.2, 89.2, 88.6, 68.1, 67.2, 26.1 and 25.2.

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