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(η^6-Arene)chromium Tricarbonyl Complexes as Chiral Auxiliaries in Asymmetric Diels-Alder Reactions

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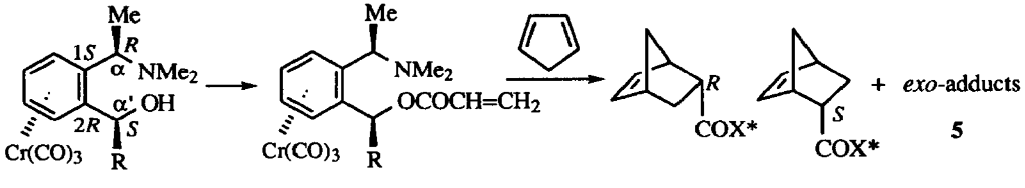
Abstract: The acrylates of chiral (1,2-disubstituted arene)chromium tricarbonyl complexes with an amine and a hydroxyl groups in the two benzylic positions were found to be serve as π-face selective auxiliaries in Lewis acid catalyzed Diels-Alder cycloadditions.

(η6-Disubstituted arene)chromium tricarbonyl complexes exist in two enantiomeric forms due to planar chirality when the arene ring is substituted in *ortho*- or *meta*-position by two different substituents. The enantiopure (η^6-arene)chromium tricarbonyl complexes have been receiving a great deal of attention as chiral auxiliaries in stoichiometric reactions[1] or chiral ligands in catalytic reactions.[2] The development of new chiral auxiliaries for asymmetric Diels-Alder reactions has also received considerable attentions.[3] The asymmetric Diels-Alder reaction of an organometallic-based chiral acrylate dienophile equivalent has been reported by employing the chiral acyl iron complex by Davies.[4] We have recently reported that the chiral chromium tricarbonyl complexes of 1,2-disubstituted arenes with amine and hydroxyl groups at the benzylic positions can be used as the ligands in catalytic ethylation of benzaldehyde[2a] and asymmetric conjugate additions to chalcone.[2b] Among these diastereomeric chromium complexes, the Ar(1*S*,2*R*),α(*R*),α'(*S*)-amino alcohol chromium tricarbonyl complexes **1** have been found to be most effective ligands for the selectivities in these asymmetric reactions. This chiral (arene)chromium tricarbonyl complex is of considerable interest not only because of its ready availability but also because of its unique structural and chemical properties. Both the benzylic hydroxyl and amino groups are directed in the *exo*-orientation due to electronic effects, and rotation is restricted about the bond between the chromium tricarbonyl complexed arene group and the carbinol carbon.[2a] As part of our ongoing research effort to develop the chiral (1,2-disubstituted arene)chromium tricarbonyl complexes in asymmetric reactions, we wish to report the asymmetric Diels-Alder reaction.

The requisite chiral acrylates **2** were easily prepared from the complexes **1**, which were obtained as major products from tricarbonyl((*R*)-*N*,*N*-dimethyl phenethylamine)chromium by diastereoselective *ortho* lithiation followed by treatment with aldehydes.[2a,5] Reaction[6] of the chiral acrylates **2** with cyclopentadiene in the presence (or absence) of 1 eq of Lewis acid in CH_2Cl_2 gave a chromatographically separable diastereomeric mixture of the *endo*-adducts **3**, **4** and the *exo*-adducts **5**. The diastereomeric ratios can be directly analyzed from 400MHz ^{1}H-NMR spectra and the reaction results are summarized in Table. In order to confirm the assignment of these product ratios, authentic samples were prepared for comparison by the coupling reaction of racemic *endo*- and *exo*-5-norbornene-2-carboxylic acids, respectively, with the chiral auxiliaries **1**. The absolute configuration of the *endo* Diels-Alder adducts was determined by conversion to the corresponding known iodolactone[7] via saponification (1.5 M LiOH in 1 : 1 H_2O/DME, reflux) and subsequent lactonization (I_2/$NaHCO_3$/H_2O). The enantiomeric excess in the *endo* cycloaddition products (**3**/**4**) was also determined by

HPLC with Chiralcel OD after conversion to the corresponding *endo* N-phenyl-5-norbornene-2-carboxamide[8] by treatment with Weinreb reagent ($Me_2AlNHPh$/benzene, reflux). The easy hydrolysis of the adducts and the efficient recovery of the chiral controllers are both noteworthy.



1 2 3 4

a; R=C_6H_5, b; R=α-naphthyl, c; R=β-naphthyl

d; R=2,4,6-$C_6H_3(Me)_3$, e; R=Et, f; R=^{i}Pr

X*=

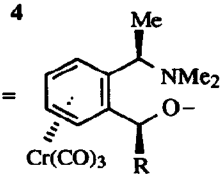


Table Asymmetric Diels-Alder Reaction of **2** with Cyclopentadiene

entry	(arene)$Cr(CO)_3$	Lewis acid	conditions °C, hrs	yield (%)	*endo* : *exo*	% de of *endo* adducts (absolute config.)
1	**2a**	none	rt, 24	90	80 : 20	74 (*R*)
2	**2a**	Et_2AlCl^a	−78, 0.5	64	95 : 5	72 (*R*)
3	**2a**	$Sn(OTf)_2$	0, 8	61	88 : 12	88 (*R*)
4	**2a**	$MgBr_2$	−30, 9	65	94 : 6	92 (*R*)
5	**2b**	$ZnCl_2$	0, 3	80	>99 : 1	>99 (*R*)
6	**2c**	$ZnCl_2$	0, 7	75	96 : 4	76 (*R*)
7	**2d**	ZnI_2	0, 3	60	>99 : 1	>99 (*R*)
8	**2e**	$MgBr_2$	0, 18	66	>99 : 1	3 (*R*)
9	**2f**	$MgBr_2$	−30, 18	58	93 : 7	2 (*R*)

[a]; Reaction was carried out by using 2.4 eq of Et_2AlCl but 1 eq of the Lewis acid resulted in no reaction.

The following facts are deducible from the reaction results. High *endo*/*exo* selectivities were obtained by Lewis acid catalyzed Diels-Alder reactions of these chiral (arene)chromium tricarbonyl complexes with cyclopentadiene. The stereochemistry of the major diastereomer under thermal conditions was identical to that obtained with Lewis acid catalyzed products. The diastereoselectivity in the *endo*-adducts (**3**/**4**) was largely dependent on the nature of substituents at the α'-benzylic position and on the Lewis acid. Highly diastereoselective Diels-Alder reactions were achieved by utilizing the (*S*)-aromatic substituted complexes at the carbinol stereocenter, especially by employment of the α-naphthyl or 2,4,6-trimethylphenyl substituted complexes **2b**, **2d** (entries 5,7). On the other hand, the (arene)chromium tricarbonyl complexes with an alkyl substituent such as ethyl or isopropyl **2e** or **2f** resulted in extremely low diastereoselectivities in the *endo*-adducts (entries 8,9).

The stereochemical course of the highly selective Diels-Alder reaction of cyclopentadiene with **2** can be interpreted as follows. The conformation of **2d** by X-ray crystallography (Fig. 1) corresponds to that of the chiral amino alcohol chromium complex[2a] **1a** which is unique auxiliary among the various effective hydroxylic chiral controllers now in wide use, e.g. 8-phenylmenthol,[9] various camphor-derived compounds,[10] and *trans*-2-phenylcyclohexanol,[11] in that the carbinol stereocenter is not contained in a ring. The conformational rigidity of the acrylate **2d** like 1-mesityl-2,2,2-trifluoroethanol[12] would be dependent on the strong electron-withdrawing ability of the $Cr(CO)_3$ group. Cyclopentadiene attacks the *si*-face of the s-*cisoid* enoate conformation of **2d** giving the *R endo*-adduct **3** under thermal conditions. In the Lewis acid catalyzed Diels-Alder reaction, an explanation for the observed diastereoselectivity is provided by a model presented in Fig. 2, which the C=O/C=C s-*transoid* conformation of the enoate part in the bidentate structure is proposed via the coordination of carbonyl oxygen *syn* to the ester oxygen with the Lewis acid. The double bond in this conformation is attacked at the less shielded *si*-face giving the *R endo*-adduct **3**. The s-*transoid* conformation in Fig. 2 is in sharp contrast to the other bidentate coordination structure in that the C=O/C=C s-*cisoid* form of the enoate moiety and is supported by X-ray data[13] and is deduced from the stereochemical analysis of the reaction products.[14] The s-*transoid* form in the coordination structure of the (arene)chromium tricarbonyl complex **2** with the Lewis acid would be attributed to π-stacking interaction between the α'-phenyl substituent and the double bond of enoate group. Indeed, the (arene)chromium tricarbonyl complexes with an ethyl or isopropyl substituent at the α'-benzylic position resulted in low diastereoselectivity due to flexible conformations in Lewis acid catalyzed Diels-Alder cycloaddition reactions.

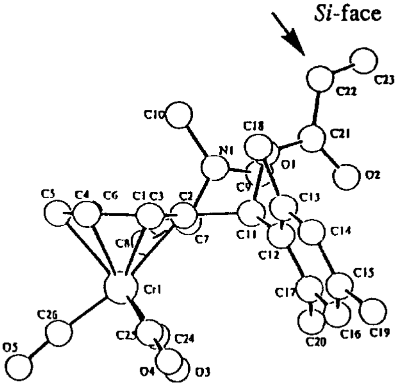


Fig. 1. Molecular structure of **2d**

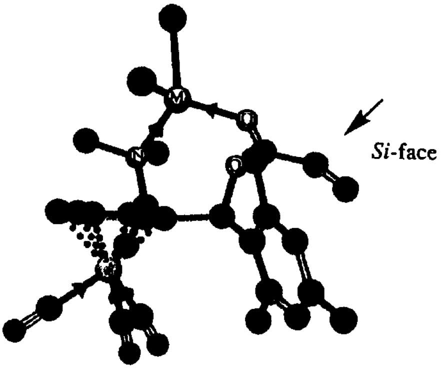


Fig. 2. Coordination structure of **2d** with MX_2

In view of the results presented above, the chiral (arene)chromium complex **2** which is easily prepared in either enantiomeric form from a commercially available phenethylamine is a good controller for Lewis acid catalyzed Diels-Alder reaction.

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6 Typical reaction: To a mixture of freshly prepared $MgBr_2$ (54mg, 0.29mmol) in CH_2Cl_2 (1 mL) was added a solution of **2a** (100mg, 0.23mmol) in CH_2Cl_2 (2 mL) at –78 °C under argon. Cyclopentadiene (0.6 mL, 7.3mmol) was added slowly to the mixture and stirred at –30 °C for 9h, and the reaction mixture was quenched with water, extracted with CH_2Cl_2. The extract was concentrated in vacuo, and a yellow residue was dissolved in small amount of ether. The ether solution was passed through short SiO_2 column followed by evaporation in vacuo to leave crude yellow crystals (75mg, 65% yield). ^{1}H-NMR analysis of the crude product revealed three diastereomers in a ratio 90.3 : 3.7 : 6.0. Purification via flash chromatography using 50% ether in hexane provided the two *endo*-adducts **3a** and **4a**. Some distinguishble characteristic protons NMR ($CDCl_3$): (*R*)-adduct; δ 1.25 (3H, d, *J*=6.7Hz, $CH\underline{Me}$), 2.16 (6H, s, $N\underline{Me_2}$), 5.71 (1H, dd, *J*=2.5, 5.5Hz, $C\underline{H}=CH$), 6.12 (1H, dd, *J*=2.5, 5.5Hz, $CH=C\underline{H}$), 6.85 (1H, s, $PHC\underline{H}O$). (*S*)-adduct; δ 1.28 (3H, d, *J*=6.7Hz, $CH\underline{Me}$), 2.14 (6H, s, $N\underline{Me_2}$), 5.91 (1H, dd, *J*=2.5, 5.5Hz, $C\underline{H}=CH$), 6.27 (1H, dd, *J*=2.5, 5.5Hz, $CH=C\underline{H}$), 6.79 (1H, s, $PhC\underline{H}O$).

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