On the Interactivity of Chiral Auxiliaries with Chiral Catalysts in the Hetero Diels-Alder Reaction: A New Route to L-Glycolipids

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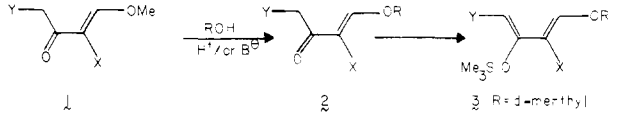
Lewis acids catalyze the cyclocondensation reactions of heterodienophiles with aldehydes.[1a] This reaction has favorable implications for the solution of a variety of contemporary and future challenges in organic synthesis. Considerable progress has been achieved in the control of relative stereochemistry[1b] and in identifying mechanistic variations[1c] of the process. More recently some possibilities for achieving enantioselectivity have been investigated.

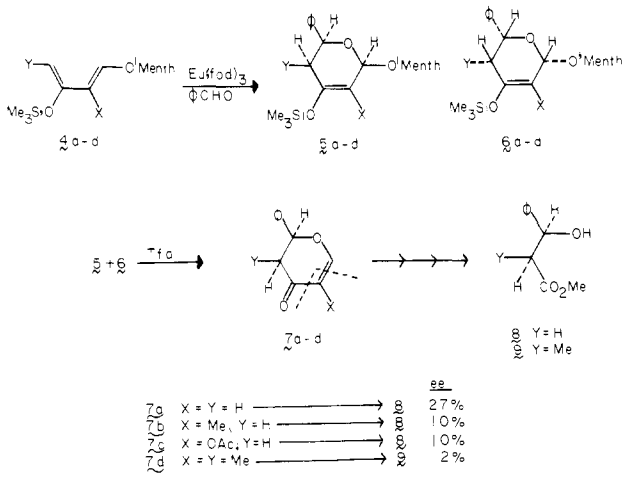
Two recent findings provided the basis for the exciting developments to be described herein. Soluble lanthanide complexes such as $Eu(fod)_3$,[2a] even in trace amounts, catalyze the cycloaddition. Included among this class of catalysts was the chiral $Eu(hfc)_3$,[2b] which, in fact, conferred some enantiotopic discrimination to the process.[3a]

Also, a wide variety of enones **2** can be synthesized from the readily available β-methoxyenones **1**, by a simply executed exchange reaction with alcohols under acidic or basic catalysis.[3b] Enol silylation of the enones **2** provides siloxy dienes, with extensive possibilities for variations of the 1-alkoxy substituent. Included among these alkoxy types, are the antipodal menthyloxy dienes **3** and **4**, which arose from the enone precursors **2**, arising from the exchange reaction of the corresponding β-methoxy enone **1**,[4] with *d*- or *l*-menthol.

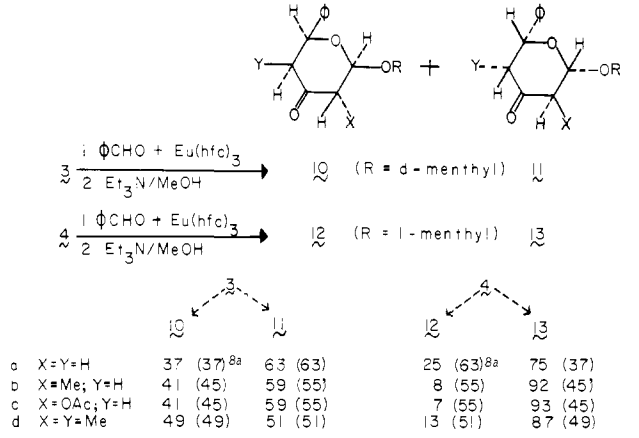


The inherent facial selectivities of the menthyloxy dienes in their reactions with benzaldehyde under achiral ($Eu(fod)_3$) catalysis were determined. In line with precedents,[1b,3a] these reactions are highly endo specific thus giving rise to two-component mixtures of **5** and **6**. The extent and sense of the facial inductions were ascertained by conversion of this mixture to quasi-racemates **7a–d**. Compounds **7a–c**, upon ozonolysis, hydrolysis of the formate, and esterification by previously described methods,[5] gave hydroxy ester **8**. Similarly, **7d** was converted to hydroxy ester **9**. The optical purities of compounds **8** and **9** were determined by NMR methods which were previously described.[3a,b] The data, shown in Scheme I, for the reactions starting with the *l*-menthyloxy dienes **4** reveal a very modest bias in favor of the "D-pyranose" products **5**, over their L-facial isomers **6**. The internal consistency of our protocols was corroborated by checking the *d*-menthyloxy dienes **3**. These exhibited an equal and opposite bias in favor of the "L-pyranose" products **6** under $Eu(fod)_3$ catalysis.

Scheme I



Scheme II. Interactivity between the Menthyl Auxiliaries and $Eu(hfc)_3$



We then examined the consequences of permuting each of the chiral auxiliaries with the chiral catalyst, $Eu(hfc)_3$. Cyclocondensation of the *d*-menthyloxy dienes **3a-d**, followed by quenching with triethylamine–methanol,[3a] afforded the corresponding facial isomers **10** and **11**. These mixtures could be directly analyzed by high-field NMR integrations of their "anomeric" protons and, in some cases, by HPLC integration. Conversion of the **10**/**11** mixtures to quasi-racemates **7**, and eventually to the hydroxy esters **8** or **9**, corroborated the extent and sense of the facial selectivity. The data are provided in Scheme II. For the sake of comparison, the facial selectivity data for the $Eu(fod)_3$ reactions of the same dienes with benzaldehyde are provided (see parentheses).

As was previously determined,[3a,b] the intrinsic enantiotopic preference of the $Eu(hfc)_3$ catalyst with achiral alkoxy groups and benzaldehyde as the heterodienophile is in the "L-pyranose" direction. Comparison of the $Eu(hfc)_3$ and $Eu(fod)_3$ diastereoselectivities in the case of *d*-menthyloxy dienes **3**, reveals little in the way of interactivity among the chiral elements.

The situation is strikingly different in the case of the $Eu(hfc)_3$-catalyzed reactions of the *l*-menthyloxy dienes **4**. These reactions, upon similar workup, afforded facial isomers **12** and **13**,[6] which were processed in the same way as the **10**/**11** mixtures.

(1) (a) Danishefsky, S.; Kerwin, J. F., Jr.,; Kobayashi, S. *J. Am. Chem. Soc.* **1982**, *104*, 358. (b) Danishefsky, S.; Larson, E. R.; Askin, D. *Ibid.* **1982**, *104*, 6457. (c) Larson, E. R.; Danishefsky, S. *Ibid* **1982**, *104*, 6458.

(2) (a) This is the trade name for tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium. (b) This is the trade name for tris-[3-((heptafluoropropyl)hydroxymethylene)-*d*-camphorato]europium.

(3) (a) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 3716. (b) Bednarski, M.; Maring, C. J.; Danishefsky, S. *Tetrahedron Lett.*, in press.

(4) The methoxy enones **1** required for the exchange reaction[3b] with the menthols to produce menthyloxy enones **2** were previously described. See: Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400 and references therein.

(5) Danishefsky, S.; Kato, N.; Askin, D.; Kerwin, J. F., Jr. *J. Am. Chem. Soc.* **1982**, *104*, 360.

(6) It was a relatively simple matter to obtain compounds **13b–d** in homogeneous form by chromatography and crystallization. Characterizations and spectral data are provided as supplementary material.

(7) For the elegant use of double diastereoselection see: Heathcock, C. H.; White, C. T. *J. Am. Chem. Soc.* **1979**, *101*, 7076.

(8) (a) The data in parentheses express the "inherent diastereofacial" bias of dienes **3** and **4** using the achiral $Eu(fod)_3$ as the catalyst. They were not obtained by direct measurement of the **10**/**11** or **12**/**13** ratios but from the e.e. data for pyrones **7a–d** given in Table I. (b) Quantitative statements about this interactivity are premature since they depend on a precise knowledge of the pertinence of $Eu(fod)_3$ as an achiral model for $Eu(hfc)_3$ and would require an "achiral model" for the menthyloxy group. (c) Izumi, Y.; Tai, A.[3] "Stereodifferentiating Reactions": Academic Press: New York, San Francisco, London, 1977; Chapter 8.

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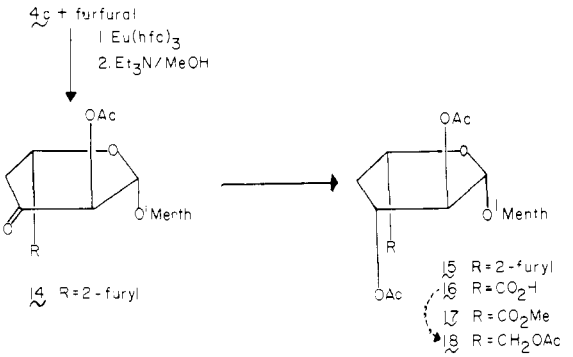
The data are provided in Scheme II. *Here, a clear interactivity of the two chiral elements is manifested. Indeed, the modest intrinsic "D-pyranose" selectivity of the l-menthyloxy auxiliary is expressed as a strong "L-pyranose" preference by intereaction with the chiral catalyst.* Thus, the increase in facial selectivity is not simply another instance of double diastereoselection,[7] in which two isolated complementary steric biases provide a mutual reinforcement. Our results involve a phenomenon[8b] wherein the inherent facial bias of the chiral auxiliary is inverted upon interaction with the chiral catalyst.

It had been recognized[8c] that, in principle, there can be interactivity between various stereo-biasing elements. Given such interactivity, overall stereodifferentiation[8c] may be quite different from the arithmetic sum of its isolated elements. The particularly novel dimension of our finding is that the interactivity is maximal when the individual biases are of *opposite* sense.

The factors that underlie this striking interactivity remain to be sorted out. Conceivably, if the basis for the phenomenon could be understood, even more discriminating combinations might be identified. However, it already seems likely that the phenomenon can play a valuable role in many kinds of synthetic objectives. We illustrate the shape of future events by the synthesis of optically pure **18** which is a β-4-deoxy-L-glucoside of *l*-menthol.

Cyclocondensation of *l*-menthyloxy diene **4c** with furfural, mediated by $Eu(hfc)_3$ in the usual way, affords a cycloadduct which was worked up with triethylamine–methanol[3a,9] (axial protonation), providing a 75% yield of the optically pure ketone **14**:[10] mp 126–127 °C; $[\alpha]^{23}_D$ + 65.2° (*c* 1.3, $CHCl_3$). Reduction of this ketone with K-selectride[11] (Aldrich) followed by acetylation provides, in 77% yield, the diacetate **15**:[10] mp 127–129 °C; $[\alpha]^{23}_D$ −5.3° (*c* 0.8, $CHCl_3$). Ozonolysis of the furan **15** afforded the 4-deoxyglucuronic acid derivative **16**, best characterized as its methyl ester **17**:[10] mp 143–145 °C; $[\alpha]^{23}_D$ −32.0 (*c* 0.6, $CHCl_3$). Reduction of **16** with borane–THF followed by acetylation afforded a 75% yield (from **15**) of **18**:[10] mp 103–105 °C; $[\alpha]^{23}_D$ −26.6 (*c* 0.7, $CHCl_3$).



Thus, the chiral auxiliary–chiral catalyst combination can be used to synthesize optically pure saccharides, including L-*glycosides, without recourse to formal resolution or glycosylation.*[13] Clearly this approach to rare and important sugars holds out considerable promise and is, accordingly, receiving close attention in our laboratory.

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Supplementary Material Available: Characterizations and spectral data for compounds **13b**, **13c**, **13d**, **14**, **15**, **17**, and **18** (1 page). Ordering information is given on any current masthead page.

(9) NMR analysis indicates an 87:13 ratio of **14** and its D-pyranose facial isomer. Compound **14** is obtained as a homogeneous entity by chromatography and crystallization.

(10) The structure of this compound is supported by spectral data which are provided as supplementary material.

(11) NMR analysis indicates the presence of ca. 9% of axial alcohol in the K-Selectride (Aldrich) reduction.

(12) For the use of a 2-furyl group as a latent carboxylic acid, see: Schmid, G.; Fukuyama, T.; Akasaka, K.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 259.

(13) For the application of the thermal hetero Diels–Alder reaction to the synthesis of a disaccharide without glycosylation, see: David, S.; Lubineau, A.; Vitale, J. M. *Nouv. J. Chim.* **1980**, *4*, 547 and references therein.

Double Oxidative Addition of β or γ Methyl Groups of Coordinated Fischer-Type Carbenes on a Triruthenium Cluster. Synthesis of $Ru_3[(\mu\text{-}H)_2,\eta^2,\mu_3\text{-}C(OEt)=C(H)](CO)_9$ and $Ru_3[(\mu\text{-}H)_2,\eta^2,\mu_3\text{-}C(OEt)N(Me)C(H)](CO)_9$

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Recent isolation of the Fischer-carbene cluster complex $Os_3[\eta^1\text{-}C(OMe)Me](\mu\text{-}H,\mu\text{-}O=CMe)(CO)_9$,[1] led us to investigate the synthesis of a triruthenium analogue; we isolate instead the two title complexes as summarized in Scheme I.

Titration of $Ru_3[\mu\text{-}H,\mu\text{-}O=C(CH_3)](CO)_{10}$ (**1**)[2] with $LiCH_3$ (1.6 N in diethyl ether) in dry, freshly distilled diethyl ether at −30 °C leads to its instantaneous conversion to the anion $[Ru_3[\eta^1\text{-}C(O)CH_3][\mu\text{-}H,\mu\text{-}O=C(CH_3)](CO)_9]^-$ (**2a**).[3] The resulting solution is warmed to room temperature and treated with 2 equiv of $C_2H_5OSO_2CF_3$.[4] IR spectra show no initial change, and 48 h of stirring is required to see the complete disappearance of the absorptions of **2a**. The solvent is removed at this point and the solid residue extracted with 30 mL of pentane. Crystallization by evaporation of the orange-red pentane extract gives orange crystals of $Ru_3[(\mu\text{-}H)_2,\eta^2,\mu_3\text{-}C(OEt)=C(H)](CO)_9$ (**3**) in 80% yield. This is summarized in the sequence **1**–**2a**–**A**–**3** in Scheme I. The molecular weight of **3** is determined by mass spectroscopy and its structure deduced from spectroscopic evidence.[5] Compound **3** is a heteroatom-substituted homologue of ethyne complexes earlier observed in the reaction of acetylenes[6] or olefins[7] with $Ru_3(CO)_{12}$. The coordinated C_2 fragment in **3** shows ^{13}C resonances at 78 and 218 ppm (with respect to tetramethylsilane); ^{13}C–H coupling of 159 Hz is observed on the 78-ppm resonance

(1) Jensen, C. M.; Lynch, T. J.; Knobler, C. B.; Kaesz, H. D. *J. Am. Chem. Soc.* **1982**, *104*, 4679–4680.

(2) Boag, N. M.; Kampe, C. E.; Lin, Y. C.; Kaesz, H. D. *Inorg. Chem.* **1982**, *21*, 1706–1708.

(3) For [Li][**2a**]: (a) IR ν_{CO} (cm^{-1}) (Et_2O) 2075 m, 2033 s, 2008 s, 1999 vs, 1968 m, 1932 m, 1571 w (η^1-acyl group), ($CHCl_3$) 1424 (μ-acyl). (b) ^1H NMR (obtained as are all other ^1H NMR reported here at 89.55 MHz) in $CDCl_3$ (ppm relative to Me_4Si) 2.70(s, 3) (μ-Co=C(CH_3), 2.41 (s, 3) η^1-C(O)CH_3, 14.46 (s, 1) Ru-*H*-Ru. (c) $\{^1H\}^{13}C$ NMR (obtained as are all other ^{13}C NMR reported here at 22.29 MHz) in $CDCl_3$ with $Cr(acac)_3$, (ppm relative to Me_4Si) 266.3 (μ-O=*C*CH_3), 249.1 (η^1-O=*C*CH_3), 202.0, 198.4, 190.9, 189.1 (CO, fluxional), 47.5 (μ-O=*C*CH_3), 41.0 (η^1-O=*C*CH_3).

(4) Gramstad, T.; Haszeldine, R. N. *J. Chem. Soc.* **1956**, 173–180.

(5) For **3**. (a) IR (petroleum ether) ν_{CO} (cm^{-1}) 2108 (w), 2080 (s), 2056 (vs), 2040 (s), 2034 (w), 2018 (m), 2013 (w), 2008 (m), 1995 (w), 1988 (vw). (b) ^1H NMR (C_6D_6, ppm relative to Me_4Si) 5.75 (s, 1, CH=), 3.49 (q, 2, OCH_2CH$_3$), 1.03 (t, 3, OCH$_2$CH_3), −17.98 (s, 2, equilibrating Ru–H–Ru). (c) ^{13}C NMR with $Cr(acac)_3$ $\{^1H\}^{13}C$ (C_6D_6, ppm relative to Me_4Si) 218 (=*C*(OEt)), 197.0, 192.6, 190.6 (CO, fluxional), 74.2 ((CH)=), 67.0 (OCH_2CH$_3$), 14.2 (OCH$_2$CH_3); off-resonance decoupled 218.0 (s), 197.0 (s), 192.6 (s), 190.6 (s), 74.2 (d), 67.0 (t), 14.2 (q); −90 °C (CD_2Cl_2, carbonyl region only) 200.9, 199.4, 196.7, 193.9, 191.2, 190.6, 189.3, 187.4, 185.6. (d) Mass spectrum, parent ion *m/e* 627 (^{101}Ru) followed by nine multiplets spaced 28 mass units apart and a large *m/e* 72 peak ([EtOCH=CH_2^+]). No higher mass signals are observed.

(6) Cetini, G.; Gambino, O.; Sappa, E.; Valle, M. *J. Organomet. Chem.* **1969**, *17*, 437–443.

(7) (a) Deeming, A. J.; Underhill, M. *J. Chem. Soc., Dalton Trans.* **1974**, 1415–1419. (b) For a recent review of other cluster complexes of these and related fragments, see: Sappa, E.; Tiripicchio, A.; Braunstein, P. *Chem. Rev.*, in press.

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