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Asymmetric Induction in Manganese(III)-Based Oxidative Free-Radical Cyclizations of Chiral Esters and Amides

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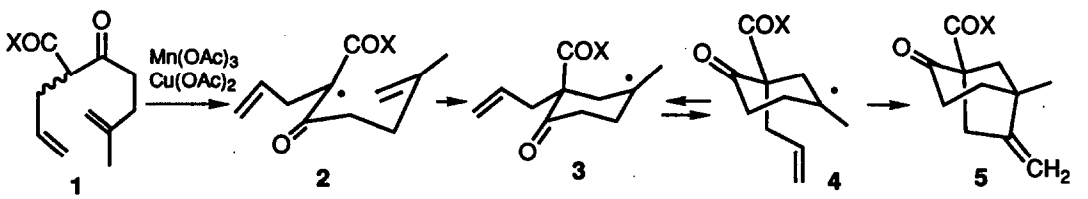
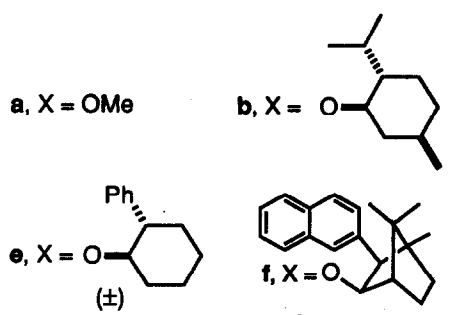
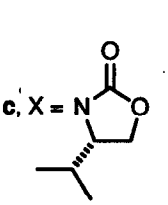
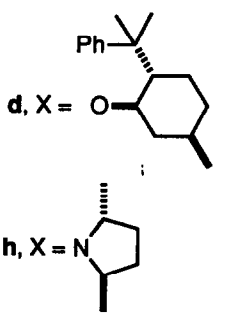
Abstract: Mn(III)-based oxidative free-radical cyclizations of phenylmenthyl acetoacetate **1d** affords 90% of **11** with 86% de. *trans*-2-Phenylcyclohexyl ester **1e** affords **5e** with only 60% de. The 2,5-dimethylpyrrolidine amide **1h** affords **14** with higher de (92%), but in only 28% yield.

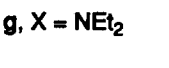
We have recently developed Mn(III)-based oxidative free-radical mono, tandem and triple cyclizations into a general route for the preparation of bicyclo[3.2.1]octan-2-ones **5a** and a wide variety of other cyclic products.[1] Since these cyclizations proceed through achiral radicals **2a** and produce chiral cyclic products **5a**, we have been interested in modifications using chiral auxiliaries that would permit these cyclizations to be carried out with asymmetric induction. Initial studies using menthyl ester **1b**, were discouraging and keto imide **1c**, obtained from Evans' chiral oxazolidinone,[2] does not undergo oxidative cyclization on treatment with Mn(III) and Cu(II) in acetic acid.[3]





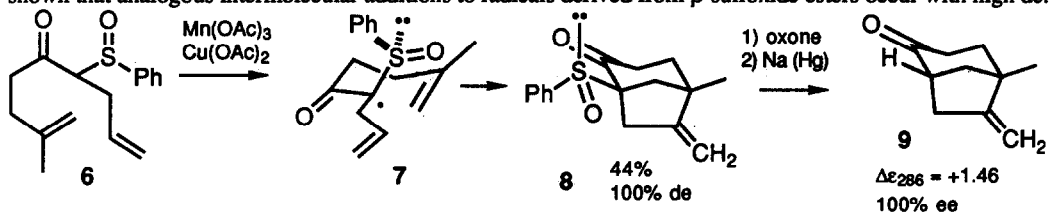






We recently reported that β-keto sulfoxide **6** can be used as a substrate for Mn(III)-based oxidative free-radical cyclization and that the sulfoxide chiral center completely controls the stereochemistry of the cyclization, which gives 44% of a single stereoisomer shown to be **8** by X-ray structure determination.[3] Cyclization of the conformer of radical **7** shown, with the S=O and C=O groups in the extended W conformation to minimize the dipole moment, should give **8** with ≈100% de since the face with a lone pair is much less hindered than the face with a phenyl group. The sulfoxide can be removed from **8** to give scalemic bicyclo[3.2.1]octanone **9** that shows the expected positive cotton effect.[5] Unfortunately, β-keto sulfoxide **6** is harder to prepare than β-keto

ester **1a**, and the yield of the cyclization of the sulfoxide **6** is much lower than with the ester **1a**. Beckwith has shown that analogous intermolecular additions to radicals derived from β-sulfoxide esters occur with high de.[4]



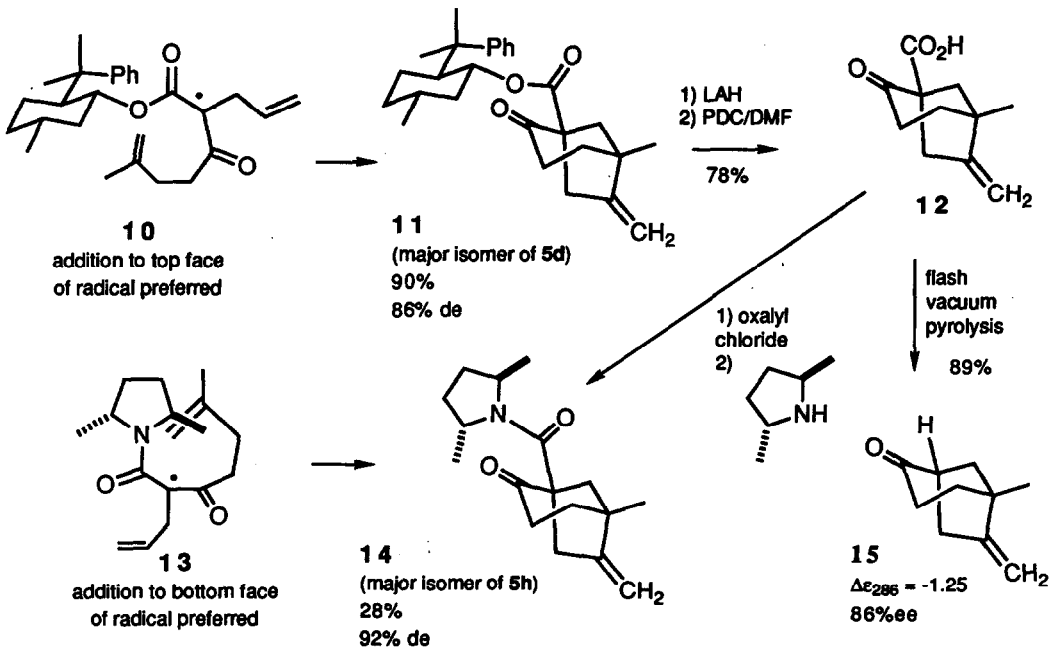
Porter, Giese and Curran have recently shown that high levels of diastereoselectivity can be obtained in the addition of chiral amide substituted radicals to alkenes. Hamon,[7] and Fang and Tsai[8] observed high levels of diastereoselectivity in reactions of 8-phenylmenthyl ester substituted radicals. We therefore decided to investigate the oxidative free-radical cyclization of a variety of ester and amide derivatives of **1** to ascertain whether chiral auxiliaries could be developed that give both high yield and high de in these cyclizations. After this work was completed, Zoretic and Caspar reported that the oxidative cyclization to give a methyleneindanone that we described[1c] can be carried out with 50% de using a β-keto imide containing Oppolzer's D-camphor sultam as the chiral auxiliary.[9]

Esters **1d**, **1e** and **1f** were obtained in >90% yield by reaction of **1a**, the appropriate alcohol[10] and 0.3-0.6 equiv of DMAP in toluene at reflux for 2-5 d as described by Taber.[11] Oxidative cyclization of a 0.1 M solution of **1d-f** in AcOH with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv of $Cu(OAc)_2 \cdot H_2O$ as previously described[1] provides **5d** (90% yield, 86% de), **5e** (89% yield, 60% de) and **5f** (87% yield, 23% de), respectively.[12] These results establish that bulky esters do not decrease the yield of the cyclization and that synthetically useful de is obtained with the 8-phenylmenthyl ester **1d**.

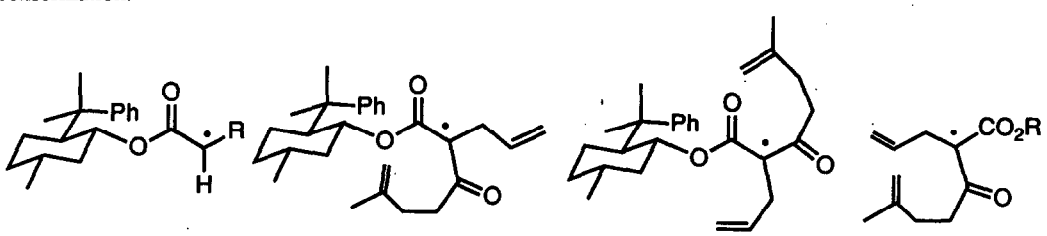
Amide **1h** was prepared in 74% yield by heating a 1:1 mixture of **1a** and (2*R*,5*R*)-2,5-dimethylpyrrolidine[13] neat at 110 °C for 4 d. Oxidative cyclization of **1h** as described above for 40 h affords only 28% of **5h** with 92% de. Since only traces of the minor diastereomer of **5h** are formed, an authentic sample of both diastereomers was prepared from **5a** to permit quantitation of the de by NMR spectral analysis. Hydrolysis of **5a** with 20% aqueous NaOH (rt, 20 h) provides the β-keto acid. Reaction of the acid with oxalyl chloride in ether at reflux affords the acid chloride that is heated with (2*R*,5*R*)-2,5-dimethylpyrrolidine in toluene at 80 °C for 30 min to give **5h** as a 1:1 mixture of diastereomers (58% from **5a**).

Although the diastereoselectivity in the cyclization of pyrrolidine amide **1h** is slightly better than with phenylmenthyl ester **1d**, the yield is much lower. Oxidative cyclization of diethylamide **1g**[14] affords only 45% of **5g** suggesting that β-keto amides are less suitable than β-keto esters for Mn(III)-based oxidative free-radical cyclizations. The high de obtained in the cyclization of **1d** and preliminary results obtained with other 8-phenylmenthyl esters suggests than 8-phenylmenthol will be a generally useful chiral auxiliary for Mn(III)-based oxidative cyclizations.

The predominant stereoisomers of **5d** and **5h** were shown to be **11** and **14**, respectively, by chemical interconversion and correlation of (-)-ketone **15** with the (+)-isomer **9** obtained from β-keto sulfoxide **8**. Saponification of 8-phenylmenthyl ester **5d** (86% de) could not be carried out analogously to that of the methyl ester **5a**. With the more hindered ester, base catalyzed retro-Dieckmann reaction[15] by attack at the ketone carbonyl group is the major process. β-Keto acid **12** was therefore prepared from **5d** in two steps. LAH reduction affords 86% of the diol as a 1.2:1 mixture of alcohol epimers and 97% of (-)-8-phenylmenthol, which can be recycled. Oxidation of the diol with PDC[16] in DMF (rt, 18 h) provides 90% of (-)-β-keto acid **12**, which is quite stable because decarboxylation must proceed through a strained enol.[17] Decarboxylation of **12** can be effected by flash vacuum pyrolysis at 450 °C to give 89% of ketone **15**. The CD spectrum establishes that **15**, $\Delta\varepsilon_{286} = -1.25$, has the opposite configuration to the ketone **9**, $\Delta\varepsilon_{286} = 1.46$, obtained from β-keto sulfoxide **8**. The difference in magnitude is consistent with 86% ee for **15**, if the ee is ≈100% for **9**.



Hamon,[7] and Fang and Tsai[8] proposed that the diastereoselectivity in additions to α-substituted phenylmenthyl ester radicals results from addition to the less hindered top face in conformer **16**. Assuming that this geometry holds in the cyclization of β-keto ester radicals, four conformers must be considered because there are two conformers about each of the bonds between the radical bearing carbon and the carbonyl groups. The two conformers shown in **18**, with the ester syn to the ketone, can be excluded since studies with alkyl substituents on the tether have established that the cyclization yields cyclohexanone **3**, with an axial ester group, as the initial product. Conformers **10** and **17**, with the ester anti to the ketone, would both yield cyclohexanone **3**, with an axial ester group, as the initial product. The formation of **11** with 86% de suggests that the double bond adds to the top face of the radical in conformer **10**. Cyclization of the radical through conformer **17** can be excluded since addition should occur from the top face to give the diastereomer of **11**. The preference for cyclization in conformer **10** may result from minimization the dipole moment with the carbonyl groups in the extended W conformation.



16
addition to top face
of radical preferred
(ref. 7,8)

10
addition to top face of
radical preferred to give **11**

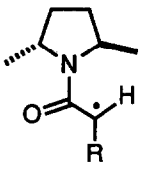
17
addition to top face of radical
would give steroisomer of **11**

18
precluded by initial
formation of cyclohex-
anone **3** with axial ester

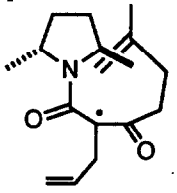
The stereochemistry of the major diastereomer of **5h** was established as **14** by preparation of an authentic sample of **14** from (-)-β-keto acid **12**. Conversion of **12** to the acid chloride and reaction of the acid chloride

with (2*R*,5*R*)-2,5-dimethylpyrrolidine as described above for the racemic acid affords **14** (88% yield, 86% de). The major stereoisomer in **14** is identical to the major diastereomer of **5h** obtained from the cyclization of **1h**.

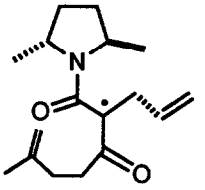
Porter, Giese and Curran proposed that the diastereoselectivity in additions to α-substituted dimethylpyrrolidine amide radicals results from addition to the less hindered bottom face in conformer **19**. The formation of **14** with 92% de could result from addition to the less hindered bottom face of radical conformer **13**. This conformer may be preferred since the carbonyl groups are in the W conformation that minimizes the dipole moment. However, there is severe steric interaction between the pyrrolidine ring and the alkenyl side chain in the transition state, so that alternate conformers need to be considered. Addition to the top face of conformer **20**, which is less hindered than **13**, would also yield **14**. Examination of models suggests that the top face of **20** may be less hindered since the α-methyl that is syn to the amide carbonyl group will interact more strongly with the approaching alkenyl side chain than the β-methyl that is anti to the carbonyl group . The β-methyl group may also force the allyl group to adopt the α-conformation further favoring attack from the top face.



19
addition to bottom face of radical preferred (ref. 6)



13
addition to bottom face of radical preferred to give **14**



20
addition to top face of radical preferred to give **14**

The selective formation of **5d** with 90% yield and 86% de establishes that 8-phenylmenthyl esters are excellent chiral auxiliaries for asymmetric oxidative free radical cyclizations. We are continuing to explore other ester groups and to explore the scope of this reaction with other substrates.

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