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ASYMMETRIC DIELS-ALDER CYCLOADDITIONS USING CHIRAL ALKYL VINYL ETHERS AND A DIENYL SULFONE

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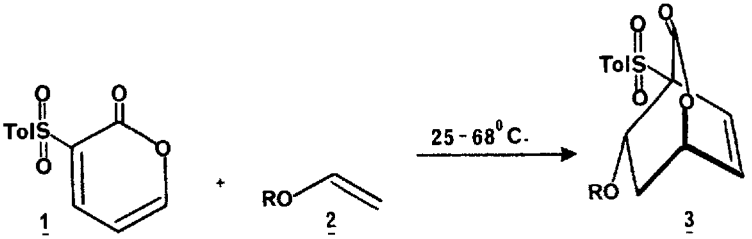
Summary: Chiral alkyl vinyl ethers 2b-2j underwent mild, inverse electron demand, Diels-Alder cycloadditions with 3-arenesulfonyl-2-pyrone 1 to form bridged bicyclic lactone adducts 3b-3j in excellent yields and with diastereoselectivities of up to 90%.

Asymmetric Diels-Alder cycloadditions are becoming increasingly useful in controlling absolute stereochemistry during formation of several carbon-carbon bonds in one reaction; by far most examples involve electrophilic, chiral dienophiles.[1] We have reported recently the first example of a highly diastereoselective Diels-Alder cycloaddition using an electrophilic, chiral dienyl sulfoxide as an enophile.[2] We have found now that electrophilic dienyl sulfone 1 undergoes some very highly diastereoselective, mild 2+4-cycloadditions with several alkyl vinyl ethers as nucleophilic, chiral dienophiles (eq. 1).[3]



(1)

	R	% Yield	% d.e.		R	% Yield	% d.e.
a	Ethyl	95	--	f	1-Naph(Me)CH	95	64
b	2-Octyl	>90	~0	g	Ph(Me)CH	75	66
c	endo-2-Bornyl	>90	~5	h	2,4,6-Me_3Ph(Me)CH	>90	80
d	8-Phenylmenthyl	>90	~5	i	Ph(i-Pr)CH	94	84
e	Menthyl	89	54	j	Ph(t-Bu)CH	90	90

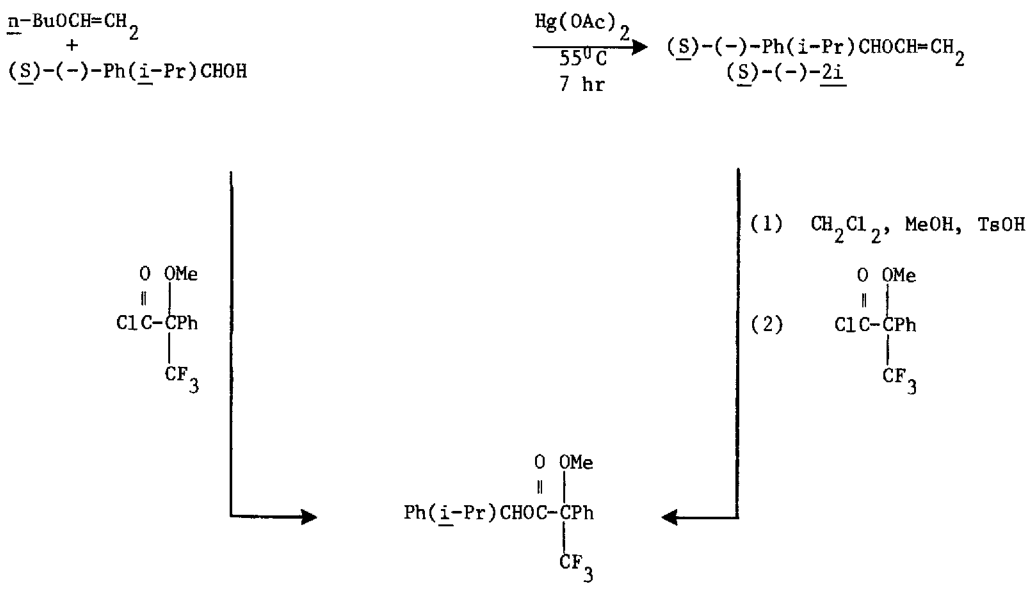
3-p-Toluenesulfonyl-2-pyrone (1), prepared from 3-bromo-2-pyrone,[4] reacted with several equivalents of various alkyl vinyl ethers 2 in methylene chloride to produce Diels-Alder adducts 3 in excellent chemical yields. No Lewis acid was needed, and no loss of carbon dioxide occurred from bridged bicyclic lactone adducts 3.[5] The structures of bicyclic lactones 3 were confirmed by IR (non-conjugated lactone) and by ^{1}H NMR (only two olefinic hydrogen atoms). That the ethoxy group in bicyclic adduct 3a is oriented toward the 2-carbon olefinic bridge is consistent with prediction based on molecular models and was determined by NMR in comparison to a structurally similar system;[6] the methyl triplet for the ethoxy group of adduct 3a appeared at δ 1.20, whereas that for the corresponding minor isomeric adduct having the ethoxy group oriented toward the 2-carbon lactone bridge (i.e., epi-3a) appeared at δ 0.86. The ratio of adducts 3a:epi-3a was >20:1.

Alkyl vinyl ethers 2b-2j, prepared from n-butyl vinyl ether and various chiral alcohols *via* mercury-promoted *trans*-etherification,[7] also underwent high-yield and mild inverse electron demand 2+4-cycloadditions (eq. 1). The diastereomeric purities of *crude* adducts 3b-3j were determined easily and accurately by 400 MHz ^{1}NMR analysis of the toluene doublets. For example, isopropyl phenyl carbinyl adduct 3i showed two tolyl doublets ($J = 8.17$ Hz) with one centered at δ 8.02 and the other centered at δ 7.92 in a diastereomeric ratio of 92:8 (84% diastereomeric excess). The pure major diastereomer was isolated after chromatography in 86% yield![8]

Although the t-butyl phenyl carbinyl adduct 3j was formed even more diastereoselectively (90% d.e.), the commercial availability of enantiomerically pure isopropyl phenyl carbinol in both (R)- and (S)-antipodes[9] and the ease of purification of diastereomeric adducts 3i prompted us to focus on adduct 3i (rather than on 3j). At this time, we can offer no unambiguous explanation for why some normally effective chiral auxiliaries (e.g., the 8-phenylmenthyl system)[10] produced such low diastereoselectivity in eq. 1. The variety of useful functional groups in adduct 3i suggests that it will be an extremely valuable and versatile intermediate for preparing various richly functionalized cyclohexyl ring systems. For example, hydroxylation of the double bond in adduct 3i followed by nucleophilic opening of the lactone ring should produce a ring-tetraoxygenated cyclohexanecarboxylic acid system.

We have converted enantiomerically pure (S)-(−)-isopropyl phenyl carbinol into the corresponding (S)-(−)-vinyl ether [(S)-(−)-2i, Scheme I]. To check that no racemization was occurring in this transetherification reaction, both the remaining alcohol and the product vinyl ether, after methanolysis, were converted into the same Mosher ester[11] derivative 4 (Scheme I). Analysis by ^{1}H and by ^{19}F NMR revealed a diastereomeric purity of >98% for the Mosher ester 4 derived from the remaining alcohol as well as from the product vinyl ether.

Scheme I



4, >98% d.e.

Enantiomerically pure vinyl ether (S)-(-)-2i was converted on gram-scale into Diels-Alder adduct (-)-3i which was isolated as a pure diastereomer in 84% yield! We are now using this chiron[12] in a planned total synthesis of some enantiomerically pure members of the shikimic acid family.[13]

Acknowledgement

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5. cf. Boger, D. L., and Mullican, M. D., J. Org. Chem., **1984**, 49, 4033, and references therein for inverse electron demand Diels-Alder reactions.

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8. A typical experimental procedure is as follows: To an argon-flushed, 10 ml, round-bottomed flask fitted with a magnetic stirrer bar and a teflon stopper was added 3-p-toluenesulfonyl-2-pyrone (0.50 g, 2.0 mmol),[4] 2-methyl-1-phenyl-1-propyl vinyl ether (0.90 g, 5.1 mmol), and dichloromethane (2.0 ml). The resulting yellow-brown suspension was stirred at room temperature, becoming homogenous after 8-9 hours. Stirring was continued until complete reaction was observed by TLC (66% ether/hexane, 2-3 days). Concentration afforded the crude Diels-Alder adduct which was analyzd by 400 MHz ^{1}H NMR and found to be a 49:1 ratio of 3i:epi-3i with 3i being a 92:8 mixture of diastereomers. Purification was by short path column chromotography (silica gel, 5% EtOAc/10% CH_2Cl_2/85% hexane) and then by PTLC (silica gel, 5% EtOAc/10% CH_2Cl_2/85% hexane, 2 elutions). The major diastereomer was recovered as a white solid (0.737 g, 1.73 mmol, 86.5%, R_f = 0.33 in 66% ether/hexane): mp 147-149°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, J=8.17 Hz, 2H), 7.43-7.26 (m, 7H), 6.97 (br d, J=7.9 Hz, 1H), 6.69 (dd, J=7.9 Hz, J=5.2 Hz, 1H), 5.04-4.94 (m, 1H), 4.65 (br d, J=7.6 Hz, 1H), 4.60 (d, J=7.6 Hz, 1H), 2.42 (s, 3H), 2.26-2.17 (m, 1H), 2.13-2.00 (m, 1H), 1.52 (br d, J=13.7 Hz, 1H), 1.09 (d, J=6.8 Hz, 3H), 0.68 (d, J=6.8 Hz, 3H); IR ($CHCl_3$) cm^{-1}: 1758, 1596, 1363, 1325, 1157, 1088. Anal. calcd. for $C_{24}H_{26}O_5S$: C, 67.57; H, 6.16; S, 7.52. Found: C, 67.45; H, 6.19; S, 7.43. The remaining product was recovered as a foam and found to be a 5:16 mixture of epi-3i:3i with 3i being a 1:16 mixture of diastereomers (0.067 g, 0.16 mmol, 8%, R_f=0.25 in 66% ether/hexane). This mixture was characterized by 400 ^{1}H NMR ($CDCl_3$). The relevant signal for epi-3i is at δ 8.12 (d, J=8.6 Hz) and for the minor diastereomer of 3i ia at δ 7.92 (d, J=8.2 Hz). In a similar fashion, (S)-(-)-alkyl vinyl ether 2i [bp_{39} 110-112°C $[\alpha]_D^{24}$ = -49° (c 1.6, $CHCl_3$)] led to lactone adduct 3i, $[\alpha]_D^{26}$ = -147° (c 0.5, $CHCl_3$), isolated as a single diastereomer in 84% yield.

9. Aldrich Chemical Company.

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