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CYCLOADDITION OF ISOQUINOLINIUM SALTS: HOMOCHIRAL TETRALINS VIA DIENOPHILES BEARING CHIRAL AUXILIARIES.

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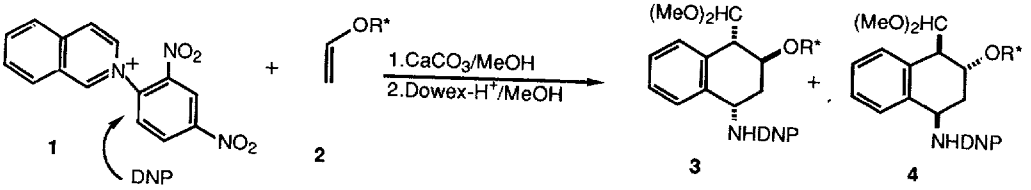
Abstract*: Inverse electron demand cycloaddition of isoquinolinium salts to dienophiles bearing chiral auxiliaries to produce homochiral tetralins are described. The optical purity of the product ranges from 5% to 95+% depending on the nature of the chiral auxiliary.*

The use of chiral auxiliaries linked to either dienes or dienophiles in the Diels-Alder reaction has become a useful method for producing homochiral cyclohexenes.[1] The logical extension of techniques for chirality transfer to cases of inverse-electron-demand cycloaddition has just begun to be developed.[2] We wish to report our results with chiral vinyl ethers, chiral vinyl acetals and chiral vinyl ortho esters as dienophiles in the Bradsher cycloaddition[3] of isoquinolinium salts to produce homochiral tetralins. The general reaction scheme is shown below, and the results of our several cycloadditions are shown in Tables 1-3.



In the case of vinyl ethers and vinyl acetals (Tables 1 and 2), the product tetralins were isolated with the chiral auxiliaries attached. Although diastereomeric excesses could be determined by comparison of integrated intensities of separate peaks in the ^{1}H nmr spectra of the crude product mixture before separation, the reported ratios are those of the isolated mixture of diastereomers. For dienophile **2c** (Table 1), only one diastereomer of the cycloadduct could be detected. For dienophile **2f** (Table 2), the only *exo* product was obtained as a single isomer. In the ortho ester examples (Table 3), the acidic methanol work-up was sufficient to cleave the auxiliaries, thus the 2-hydroxytetralin was isolated directly. The enantiomeric excesses were determined by making the Mosher ester derivative of hydroxy tetralin and examining their ^{1}H nmr spectra.[4]

It is interesting that the auxiliaries which afford the greatest face selectivity in the inverse-electron-demand cycloaddition have phenyl groups. Modelling of possible interactions of the proximate phenyls with the dienophilic double bond and/or with the isoquinolinium salt would be premature at this stage of our work.[5] Another point of interest in the acetal series is that we observe far superior selectivity with the α-vinyl tetrabenzyl-D-glucoside **2f** than with the β–vinyl glucoside **2g**. This selectivity order is opposite to that observed for Diels-Alder reactions of α– and β- dienyl tetraacetyl-D-glucosides reported by

TABLE 1

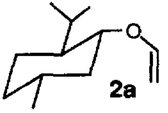
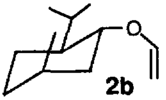
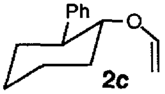
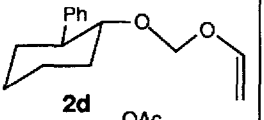
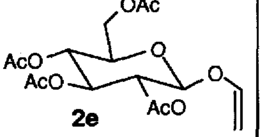
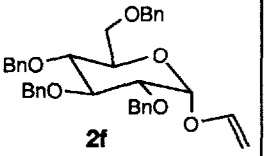
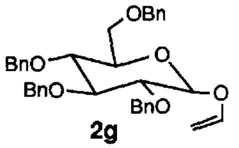
Entry	Dienophile	Major Diastereomer	Yield	de
a	 **2a**	**4**	57%	36%
b	 **2b**	**4**	56%	10%
c	 **2c**	**4**	91%	95+%

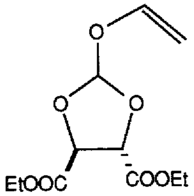
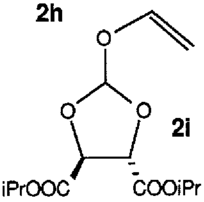
TABLE 2

Entry	Dienophile	Major Diastereomer	Yield	de
d	 **2d**	**4**	62%	55%
e	 **2e**	**3**	31%	33%
f	 **2f**	**3**	70%	95+%
g	 **2g**	**3**	40%	50%

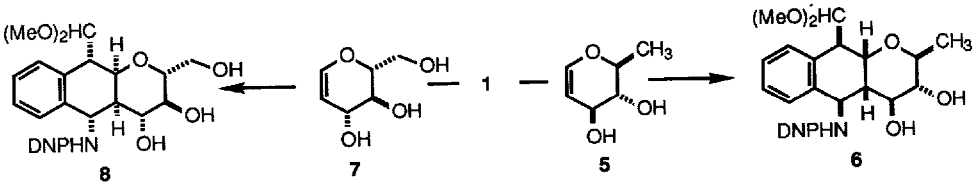
Stoodley.[6] To our disappointment, chiral ortho ester vinyl ethers **2h** and **2i** give a poor diastereoface selection, whereas the reaction of tartarate modified allyl boronate of analogous geometry affords very high diastereoface discrimination in a metallo-aldol reaction.[7]

Our configurational assignments are based on comparisons of CD spectra of the products with CD's of tricyclic tetralin adducts **6** and **8** prepared from sugars **5** and **7** of known configuration. We observe equal and opposite Cotton effects at 237 nm, (-) for **8** and (+) for **6** , which we ascribe to an interaction between the 2,4-dinitrophenylamino chromophore and the adjacent benzene ring.[8] A complete

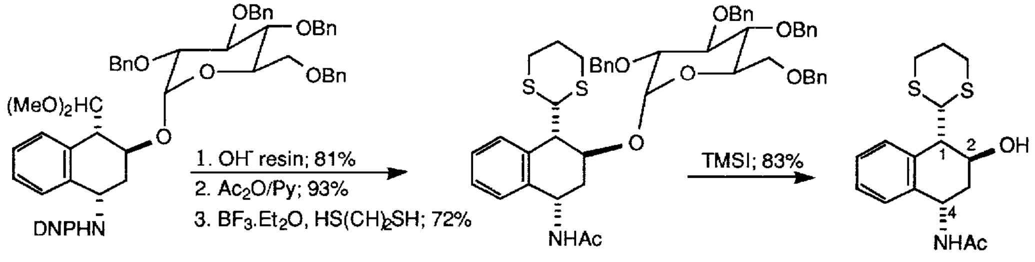
TABLE 3

Entry	Dienophile	Major Enantiomer	Yield	ee
h	 **2h**	**3** $R^* = H$	48%	16-20%
i	 **2i**	**3** $R^* = H$	68%	5-11%

analysis of their nmr spectra leaves the assignment of relative, and hence absolute configurations unambiguous. Since all the tetralins in Tables 1-3 have the same chromophoric pair, we assigned the configuration of the major product isomer of each cycloaddition by examining the sign of its Cotton effect at 237 nm. It appears that the remote aryl groups of the chiral auxiliaries do not interfere with the principal chromophore interactions. The separated diastereomers **3** and **4** from entry g (Table 2) exhibited opposite Cotton effects at 237 nm, even though the tetrabenzyl-D-glucose portion of the auxiliary is identical in both cases.



In order to develop a useful synthesis of chiral tetralins, it is necessary to remove the chiral auxiliary from product **9** (entry f, Table 2). Although tetrabenzyl α-D-glucosides are hydrolyzed with some difficulty, a straightforward sequence shown below is practical. Thus, cleavage of the 2,4-dinitrophenyl group and acetylation of the free amine is followed by the formation of the dithiane **10.** Then the glucoside link is easily cleaved with TMSI affording chiral tetralin **11** in 45% overall yield from **9.** Recently, Meyers[9] has used an asymmetric addition to an oxazoline derivative of naphthalene to generate two chiral centers on a dihydronaphthalene which was ultimately converted to a homochiral tetralin with chirality at carbons 1,2 and 4. Also Charlton's[10] asymmetric photocycloaddition of α-hydroxy orthoquinonedimethanes to chiral dienophiles provides a versatile route to substituted homochiral tetralins. For many tetralins, our variant of the Bradsher cycloaddition will be competitive with these approaches.[11]



9 **10** **11**

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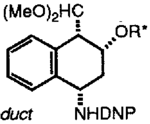

endo product

5. (a) see footnote 24 of Evans, ref. 1 (c) for an up-to-date bibliography of examples of aromatic ring shielding in diastereoselective Diels-Alder cycloadditions; (b) Whitesell, J.K.; Lawrence, R. M.; Chen, H. H. *J. Org.Chem.* **1987**, *51*, 4779. (c) Oare, D. A.; Heathcock, C.H. *Chemtracts.* **1988**, *1*, 376.

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