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The Use of 1,2-*trans*-Cyclohexanediol as an Efficient Chiral Auxiliary for the Asymmetric Cyclopropanation of Allylic Ethers

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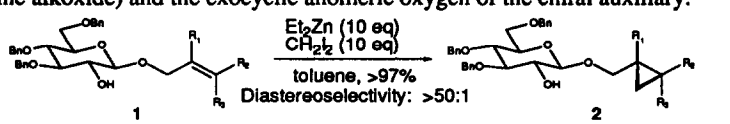
Abstract: A new and simple chiral auxiliary derived from optically pure 1,2-*trans*-cyclohexanediol was developed for the asymmetric Simmons-Smith cyclopropanation of substituted allylic alcohols. Excellent yields and diastereoselectivities were obtained with a variety of olefins.

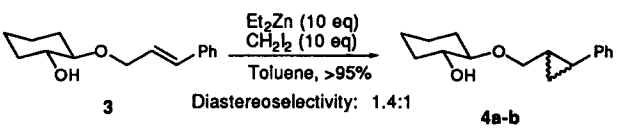
We recently reported that 3,4,6-tri-*O*-benzyl-D-glucose could be used as an efficient and practical chiral auxiliary for the cyclopropanation of a variety of substituted allylic alcohols (eq 1).[2] Preliminary observations seem to indicate that the extremely high level of asymmetric induction in that reaction can be attributed to a unique complexation between the two-point binding chiral auxiliary and the bis(iodomethyl)zinc reagent.[3] It is believed that precomplexation of the bis(iodomethyl)zinc reagent with the substrate involves the C-2 oxygen (in the form of a zinc alkoxide) and the exocyclic anomeric oxygen of the chiral auxiliary.[4]



(1)

To further study the mechanism of the interaction between the reagent and the chiral auxiliary, we needed a simpler model that would bear fewer oxygen atoms. We became intrigued by the possibility of using the readily available, optically pure 1,2-*trans*-cyclohexanediol as a simple chiral auxiliary[5] since it possessed all the structural requirements that were thought to be necessary for observing high diastereoselectivities in that reaction. The low molecular weight of the auxiliary along with the availability of both enantiomers[6] made it an attractive, synthetically-useful surrogate to the sugar-based auxiliary. In this paper, we wish to report that although the behavior of 1,2-*trans*-cyclohexanediol is substantially different from that of the glycoside in the cyclopropanation reaction, it can be used as an extremely useful and viable alternative.[7]

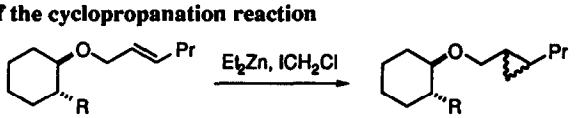
Quite unexpectedly, a 1.4:1 diastereomeric mixture of cyclopropanes was obtained in almost quantitative yield (>95%) when the cinnamyl-derived alcohol was submitted to the standard conditions developed in the sugar series (eq 2).



(2)

This surprising result prompted us to carefully investigate the reaction conditions to improve the diastereoselectivities. It was found that for this particular system, a high level of stereochemical induction (>20:1) could be obtained if bis(chloromethyl)zinc[8] was used instead of bis(iodomethyl)zinc (Table 1, entry 1-3).[9] The use of 3 equivalents of the reagents in toluene was found to be optimal for obtaining quantitative yields and excellent diastereoselectivities. This observation is contrary to what is generally observed with the sugar-derived auxiliary. Typically, the diastereoselectivities are usually similar or lower when glycosides **1** are treated with bis(chloromethyl)zinc instead of bis(iodomethyl)zinc. The reaction shows some dependence on the nature of the solvent used. Although the yields and diastereoselectivities were relatively good in other non-coordinating solvents such as CH_2Cl_2 and $ClCH_2CH_2Cl$, these were abandoned due to their propensity to promote formation of small amounts (5-10%) of a by-product resulting from the methylation of the zinc alkoxide (entry 5,6). The use of coordinating solvents led to much lower yields of the cyclopropane products (entry 7-9). As expected from previous observations, the protection of the secondary alcohol was also detrimental to the diastereoselectivities (entry 10-13). As in the sugar series, this illustrates the unique ability of the zinc alkoxyde formed *in situ* to participate in the delivery of the reagent.

Table 1. Optimization of the cyclopropanation reaction



5 **6a-b**

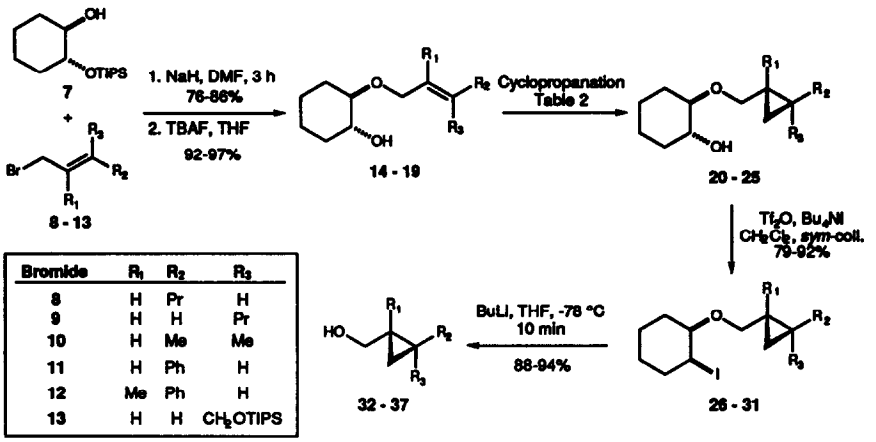
Entry	R	Et_2Zn (eq)	ICH_2Cl (eq)	Solvent	temp (°C)	time (h)	yield[a] (%)	ds[b] (%)
1	-OH	2.0	2.0	Toluene	-20	3.0	68	>20:1
2	-OH	3.0	3.0	Toluene	-20	3.0	>97	>20:1
3	-OH	3.0	3.0	Toluene	-20	18.0	81	>20:1
4	-OH	5.0	5.0	Toluene	-20	3.0	88	>15:1
5	-OH	3.0	3.0	$(ClCH_2)_2$	-20	5.0	92	15:1
6	-OH	3.0	3.0	CH_2Cl_2	-20	5.0	90	15:1
7	-OH	3.0	3.0	Et_2O	-20	5.0	54	>18:1
8	-OH	3.0	3.0	THF	-20	5.0	<5	---
9	-OH	3.0	3.0	DME	-20	5.0	0	---
10	-OMe	5.0	5.0	Toluene	-20→0	2.5	97	1.6:1
11	-OAc	5.0	5.0	Toluene	-20	1.0	85	5.3:1
12	-OBn	5.0	5.0	Toluene	-10	1.0	>95	1.5:1
13	-OTBDMS	5.0	5.0	Toluene	-20	1.0	>95	1.3:1

[a]The yields were determined by ^1H NMR analysis of the crude material. [b]The diastereoselectivities were obtained by ^1H and ^{13}C NMR by comparison with an authentic 1:1 mixture.

With the optimized conditions in hand, the scope of the reaction was then established (Table 2). The installation of the chiral auxiliary could be achieved in excellent yields (74-86%) by alkylation of optically pure monoprotected diol **7**[10] with the desired allyl bromide (**8-13**) (Scheme 1). A subsequent fluoride-mediated

desilylation produced the precursor to the cyclopropanation reaction.[11] As shown in Table 2, the diastereoselectivities and the yields obtained for the asymmetric cyclopropanation reaction were excellent (>20:1, ≥90%) for a variety of substituted allylic alcohols.[12]

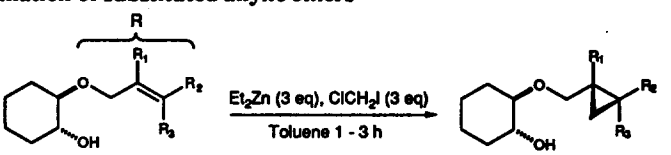
Scheme 1



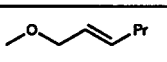
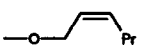
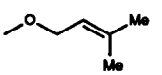
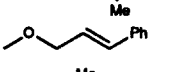
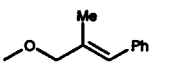
Bromide	R_1	R_2	R_3
8	H	Pr	H
9	H	H	Pr
10	H	Me	Me
11	H	Ph	H
12	Me	Ph	H
13	H	H	CH_2OTIPS

The cleavage of the chiral auxiliary could then be smoothly accomplished in high yield by initial iodide formation[13] and subsequent BuLi-induced β-elimination.

Table 2. Cyclopropanation of substituted allylic ethers



14 - 19 → 20 - 25

Compound	R	temp (°C)	Yield (%)[a]	ds[b]
14		-30	98	21:1
15		-20	97	24:1
16		-30	98	23:1
17		-20	97	24:1
18[c]		-10→0	90	15:1[d]
19[e]		-20	95	>20:1[d]

[a]Isolated yields of analytically pure compounds. [b]The diastereoselectivities were determined by ^{13}C NMR and by capillary GC analysis of the cleaved cyclopropylmethanol. [c]5 equivalents of the reagents were used in this case and the reaction mixture was stirred for 16h at 0 °C. [d]Determined by ^{13}C NMR only. [e]5 equivalents of the reagents were used in this case.

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10. Prepared in 87% yield from optically pure diol upon treatment with TIPSOTf (1.05 eq), Et_3N (1.1 eq) in CH_2Cl_2.
11. Compound **19** was prepared by selective monosilylation of the corresponding diol produced after the fluoride-mediated bis desilylation.
12. The absolute stereochemistry of the cyclopropane was firmly established by comparing the $[\alpha]_D$ of the cleaved material with authentic samples.
13. Based on a modification of the Binkley's protocol: Binkley, R. W.; Ambrose, M. G.; Hehemann, D. G. *J. Org. Chem.* **1980**, *45*, 4387-4391.

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