



## Diastereo-differentiating intramolecular cyclopropanations of prochiral olefins and a diazo ester linked by optically active 2,4-pentanediol

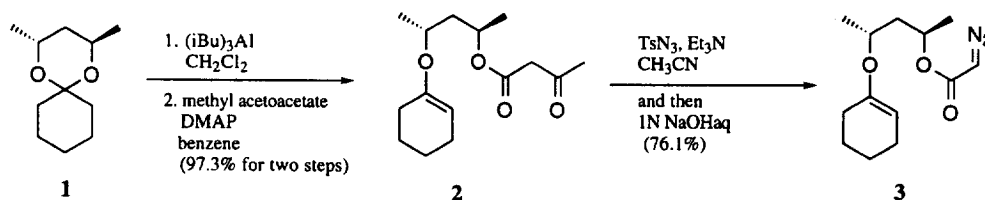
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**Abstract:** Intramolecular cyclopropanation of **3**, the substrate having a chiral auxiliary as a linking bridge between a diazo ester and cyclohexene, was found to give the cyclopropane **4** having over 99% diastereomeric excess (d.e.) in 91.5% yield. The reaction was also carried out at 138°C (*p*-xylene reflux) to give **4** of 88.2% d.e. © 1997 Elsevier Science Ltd. All rights reserved.

We have reported several diastereo-differentiating reactions using optically active 2,4-pentanediol (PD) as a chiral linking bridge between prochiral olefins and reagents: cyclopropanation with zinc carbenoid,<sup>1</sup> epoxidation,<sup>2</sup> and photocycloaddition with an excited phenyl group.<sup>3</sup> In all cases, the diastereofaces of the prochiral olefins were well differentiated by the reagents to afford products having extremely high diastereomeric purity. Thus, PD is a simple, small, and flexible molecule, but its bidentate nature promotes high diastereo-differentiation in intramolecular reactions. In this communication, we report our examination of intramolecular cyclopropanations of prochiral olefins and a diazo ester to demonstrate the stereo-differentiating ability of our reaction design. By this cyclopropanation reaction, we were also able to introduce two functional groups on the optically active cyclopropane rings.

The diazo ester **3** was prepared in four steps: (1) acetalization of cyclohexanone and PD (82.9% yield), (2) isomerization with triisobutylaluminium, (3) esterification with methyl acetoacetate catalyzed by dimethylaminopyridine (97.3% for 2 steps),<sup>4</sup> and (4) introduction of a diazo group with tosyl azide and triethylamine followed by aqueous sodium hydroxide (76.1%)<sup>5</sup> (Scheme 1).



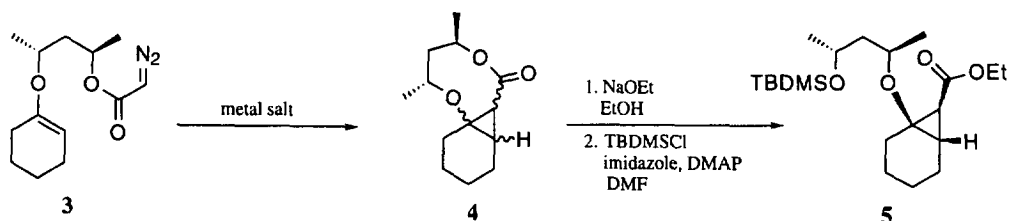
Scheme 1.

Intramolecular cyclopropanation of **3** in benzene by warming to reflux proceeded smoothly (nitrogen gas was evolved around 50°C) to produce the cyclopropane **4** in 91.5% yield after isolation by flash chromatography. In order to determine the d.e. of **4**, the reaction mixture of **4** was converted into **5** in two steps (Scheme 2). Capillary GLC analysis of the obtained **5** showed a single peak. Independently, a mixture of four diastereomers of **5** was prepared by intermolecular cyclopropanation, and its analysis by capillary GLC under the same conditions showed four peaks. From these experiments, it was

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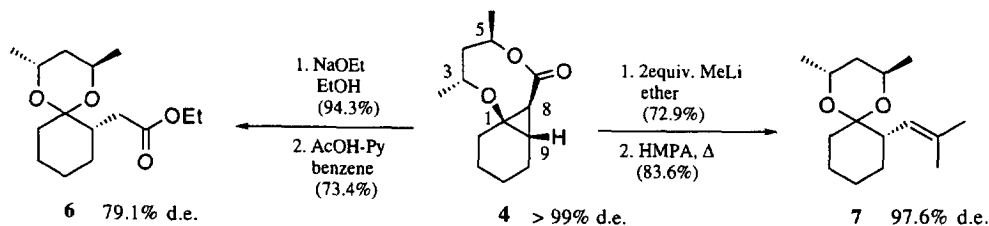
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determined that the d.e. of **4** was over 99%. Cyclopropanation of **3** with  $\text{CuSO}_4$  in the presence of a chelating agent, EDTA or TMEDA, also produced **4** as a single diastereomer. The reactions of **3** with  $\text{Cu}(\text{acac})_2$  in benzene (room temperature to reflux) and with  $\text{Rh}_2(\text{OAc})_4$  in  $\text{CH}_2\text{Cl}_2$  (room temperature) gave diastereomeric pure **4** in 78.1% and 60.7% yields respectively.<sup>6</sup> These results show that the high diastereo-differentiation does not depend on the nature of the carbenoid but is attributed to the stereochemistry of the PD moiety. When the reaction was carried out at high temperatures by the addition of **3** to a refluxing slurry of  $\text{CuSO}_4$  in the stated solvent, the d.e.'s of the obtained **4** decreased to 98.0% (80°C, benzene reflux), 92.2% (110°C, toluene reflux), and 88.2% (138°C, *p*-xylene reflux).



Scheme 2.

The stereochemistry of **4** was determined to be (1*R*, 8*S*, 9*S*) by the following chemical transformations. Treatment of **4** with sodium ethoxide in ethanol followed by acid-catalyzed opening of the cyclopropane ring resulted in **6** of 79.1% d.e.,<sup>1e,7</sup> and its spectrum was identical with the (*R,R*)-PD acetal of (–)-(2*S*)-ethyl 2-oxo-cyclohexanacetate (Scheme 3).<sup>8</sup>



Scheme 3.

An alternative reaction could be carried out in keeping the stereochemical purity at the 9-position of **4**. Addition of **4** with excess methyl lithium followed by dehydration at 180°C in hexamethylphosphoramide (HMPA)<sup>9</sup> gave **7** of 97.6% d.e.<sup>7</sup> (Scheme 3).

The present diastereo-differentiating cyclopropanation was also successfully applied to the following cyclic and acyclic substrates (Figure 1). All the reactions gave the corresponding products in diastereomeric pure forms, and the isolated yields were 55.2%, 63.5%, 54.6%, 22.4%, and 39.1% from **8**, **9**, **10**, **11**, and **12** respectively.

In the present reaction, it was found that the diastereoface of olefin to be attacked was the *si-re* face, the same as in previously reported other reactions using PD as a linking bridge. An expected structure of the reaction transition state of the *si-re* face attack is shown in Figure 2-A. In the structure,

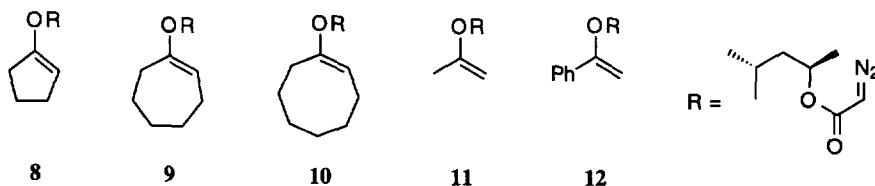


Figure 1.

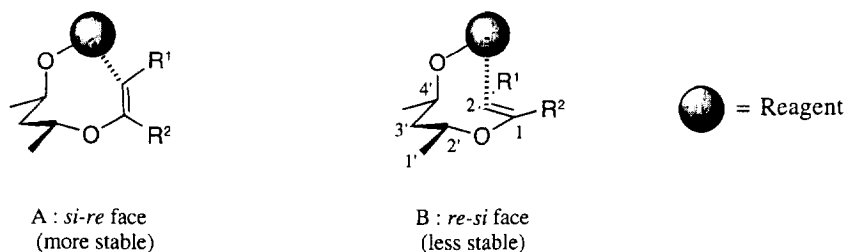


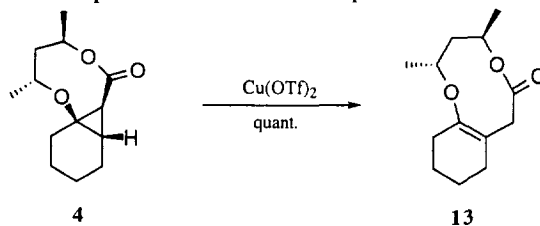
Figure 2.

the two methyl groups of the PD moiety have anti-periplanar conformation. With retention of the conformation of the PD moiety, it is also possible to make an alternative structure, Figure 2-B, in which the reagent attacks from the *re-si* face of olefin. The experimental results of the predominant *si-re* face attack can be explained by the steric repulsion between 4' and 2 protons in Figure 2-B.

The present cycloaddition proceeded under complete diastereoface-differentiation giving only the *cis*-isomer.<sup>10</sup> Since cyclopropanes having ether and ester groups can convert to various compounds,<sup>11</sup> the obtained products are considered to be promising chiral synthons. Further studies to prove the versatility and applicability of the present reaction design to other types of diastereo-differentiating reactions are now in progress.

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- The reaction of **3** with Cu(OTf)<sub>2</sub> in ether at room temperature gave **4** in only 12.9% yield, because the produced **4** was further reacted under the reaction conditions and converted to **13**. The reaction with Cu(OTf)<sub>2</sub> in benzene by warming to reflux gave only **13**, and the reaction catalyzed by Pd(OAc)<sub>2</sub> in ether at room temperature afforded a complex mixture.



- The d.e.'s of **6** and **7** were determined by capillary GLC (OV-1, 25 m). The authentic samples of the mixtures of their diastereomers were synthesized from the corresponding racemic ketones and PD.
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