Diastereo-Differentiation during 2,4-Pentanediol Tethered Simmons-Smith Type Cyclopropanation: Reaction Species of Hydroxyl Group Directed Zinc Carbenoid Addition

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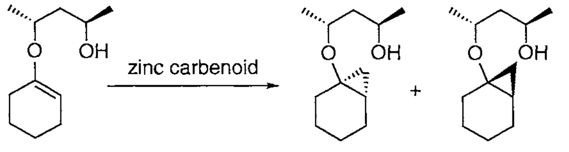
The predominant formation methods for the diastereo-differentiating species of zinc carbenoid addition to the 1-cyclohexenyl ether carrying the 2,4-pentanediol moiety were established. The species were found to include two zinc atoms and one carbenoid carbon at the hydroxyl group.

We have been studying asymmetric reactions based on a design where 2,4-pentanediol (PD) acts as a chiral tether between a prochiral reactant and a reagent.[1] During the intramolecular reaction of a reactive species produced from the reagent moiety with the reactant moiety, the two chiral centers on the tether part effectively control the stereochemical fate of the reactant moiety resulting in a product of over 99% diastereomeric excess (de). One of the variants is in situ formation of a bonding between an active species and the hydroxyl group in the PD moiety prior to the intramolecular reaction.[2,3] As the PD tethered *quasi*-intramolecular reaction is not so favorable in an activation entropy factor as the similar diastereo-differentiating reactions of allylic alcohols, it is essential to control the concentration and the reactivity of the free species in order to predominantly cause these intermolecular reactions. As such an example, we have demonstrated the diastereo-differentiating cyclopropanation to an olefin with zinc carbenoid represented by the reaction of **1** shown in Scheme 1.[2] When diiodomethane (10 equivalents) was added to a solution of **1** and diethylzinc (5 equivalents) in a polar ether, THF or DME, **2a** was obtained as the major product in 94% de (56% yield) or 95% de (65% yield), respectively. Only by changing the solvent to ethyl ether having a lower polarity, **2a** became a minor diastereomer resulting in –8% de (73% yield). The strong de dependence could not be reasonably explained by the change of the diastereo-differentiating ability of the PD tethered *quasi*-intramolecular reaction, but the contribution of the intermolecular reaction with free carbenoids can be responsible. In this study, we investigated the product analysis of the reaction of **1** under varied reaction conditions to determine the predominant formation method and the structure of the diastereo-differentiating zinc carbenoid species.



1 **2a** **2b**

Scheme 1.

We first investigated the de dependence on the conversion of **1** to **2**. The reactions in ethyl ether and DME were interrupted before the completion of the reaction, and the reactant/product ratio and the product de were determined by GLC analysis using an ODS capillary column. These results are shown in Figure 1. The de's in both the solvents were higher at the early stage of the reaction, and then slightly decreased in DME but drastically decreased in ethyl ether. The results indicated that in ethyl ether, the major product was switched from **2a** to **2b** during the reaction.

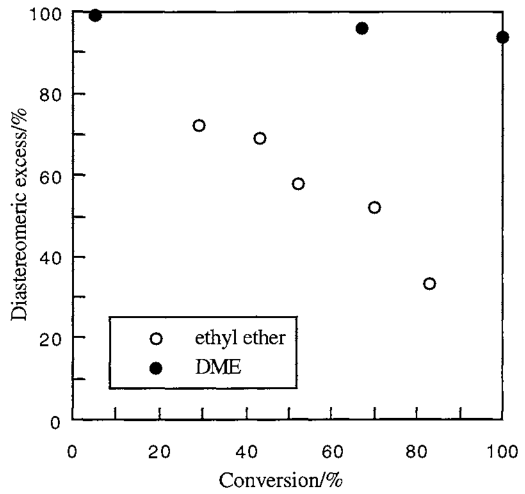


Figure 1. Diastereomeric excess of **2** as a fanction of convertion of **1** during the reaction in ethyl ether and DME.

To separate the reaction steps, the formation of zinc carbenoid and its addition to the olefin in **1**, zinc carbenoid was prepared by mixing diethylzinc and diiodomethane before the addition to **1**. The produced species are formally expressed as $EtZnCH_2I$ from a 1 to 1 mixture and $Zn(CH_2I)_2$ from a 1 to 2 mixture. The results are summarized in Table 1. Independent of the solvent used, the de was 95–96% with $EtZnCH_2I$, whereas the de slightly varied with $Zn(CH_2I)_2$ in the range of 90–95%. These high de's in contrast to the results by the regular method were only explainable by the reactive intramolecular species including more than two zinc atoms. This expectation is also supported by the fact that the addition of zinc iodide to the regular method drastically increased the formation of **2a** in the reaction with ethyl

Table 1. The product yield and de obtained by addition of a mixture of Et_2Zn and CH_2I_2

Entry	Solvent	Et_2Zn	CH_2I_2	Reaction time/h	de/ %	Yield/ %
1	ethyl ether	5	10	1.5	95	59.5
2	ethyl ether	5	5	1.0	96	62.6
3	THF	5	10	1.5	90	14.5
4	THF	5	5	3.5	96	56.0
5	DME	5	10	2.0	93	18.6
6	DME	5	5	1.5	95	30.7

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ether.[2b]

Since the prepared solution of zinc carbenoid was gradually decomposed during the addition, the required amounts of the reagents to allow the reaction could not be determined by the above experiments. To estimate the conditions having just enough reagents to allow the reaction, diiodomethane was added to a mixture of **1** and diethylzinc as slow as the cycloaddition process. Under these conditions, the excess carbenoids are reduced to a minimum. As shown in Table 2, the required amounts of reagents are two equivalents of diethylzinc and one equivalent of diiodomethane in ethyl ether. In THF, more reagents are required to perform the cycloaddition, presumably because inactivation of the carbenoids due to strong solvation of the zinc atom. It should be noted that the reaction in ethyl ether with minimum amounts of the reagents (entry 2) resulted in the best results of 97% de.

Table 2. The product yield and de obtained by slow addition of CH_2I_2

Entry	Solvent	Et_2Zn	CH_2I_2	Addition time/h	de/ %	yield/ %
1	ethyl ether	4	3	6.5	96	92.4
2	ethyl ether	2	1	1.0	97	61.5
3	ethyl ether	1	1	1.0	–	0[a]
4	ethyl ether	1	2	2.0	–	0[a]
5	THF	4	3	3.5	94	63.6
6	THF	2	2	2.0	–	0[a]
7	THF	2	1	1.0	–	0[a]
8	THF	1	1	1.0	–	0[a]

[a] No reaction after the addition and the reactant **1** gradually changed to the corresponding acetal.

The required amounts of the reagents were further confirmed by the following experiments. When **1** was added to a 1 to 1 mixture of diethylzinc and diiodomethane in ethyl ether, the reaction did not occur at all, but when another equivalent of diethylzinc was added to this mixture, the product with a 96% de was obtained in 41.5% yield. Thus, it was assumed that the species of **3** is inert but **4** or **5** produced by the addition of diethylzinc reacts with high diastereo-differentiation. The reaction of **1** with zinc-copper and diiodomethane in ethyl ether also resulted in a **2a** rich product (87% de). In this case, the most of the reaction is expected to proceed through species **6**; one $ZnICH_2I$ reacts with the hydroxyl group releasing CH_3I and another one coordinates to form the reactive species **6**. To support this model, the species formally expressed as **7** or **8** was prepared. That is, **1** was treated with sodium hydride followed another one coordinates to form the reactive species **6**. To support this model, the species formally expressed as **7** or **8** was prepared. That is, **1** was treated with sodium hydride followed by the addition of zinc iodide to make the zinc iodide salt of **1**. To the mixture, one equivalent each of diethylzinc and diiodomethane were added. From this reaction, the cyclopropane of 96% de was obtained in 45.6% yield.

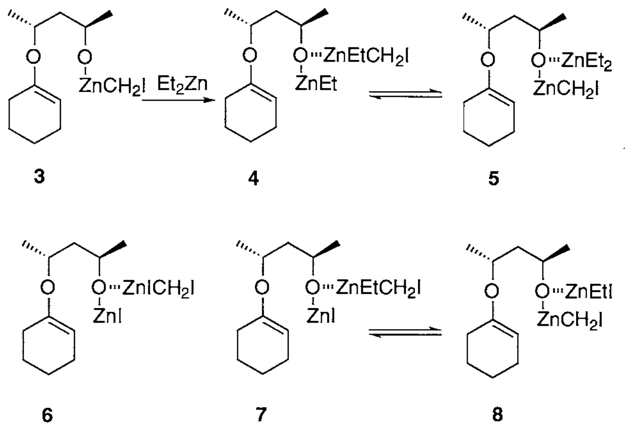

Figure 2.

In this study, we determined the reaction conditions to perform the predominant *quasi*-intramolecular zinc carbenoid addition to **1** independent to the solvent used. It was also disclosed that the reactive species placed at the hydroxyl group includes two zinc atoms and one carbenoid carbon, of which the structure was in good agreement with the estimated ones for the other reaction systems.[4,5] The importance of the present results in zinc carbenoid chemistry is that the yield and the de of the reaction of **1** was very sensitive for the reaction conditions and that the product analysis resulted in an adequate assumption for the structure of the reactive species. In addition to the present results, detailed kinetic studies of variations of the zinc species during the reaction will promote an understanding on the overall mechanism of the present system.

References and Notes

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