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Hydroxy direction of zinc carbenoid addition to a remote olefin. Analysis and improvement of 2,4-pentanediol tethered Furukawa cyclopropanation

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Abstract—Zinc carbenoid addition to an olefin stereocontrolled by a chiral and remote intramolecular hydroxy group was studied in detail. Stereoselectivity as well as chemical yield of the Furukawa cyclopropanation was dramatically improved by modifications of the procedure of addition of the reagents. The structure of an active species to give the hydroxy-directed product is proposed. © 2001 Elsevier Science Ltd. All rights reserved.

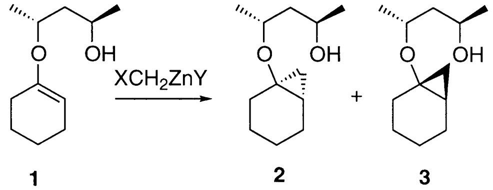
1. Introduction

Hydroxy group-directed zinc carbenoid addition to an olefin is a promising method for constructing a cyclopropane ring under strict regio- and diastereo-control.[1] The reactions can be performed easily just by adding diiodomethane to a mixture of the substrate and activated zinc (Simmons–Smith reaction[2]) or diethylzinc instead of activated zinc (Furukawa procedure[3]). However, when the hydroxy group to direct the cyclopropanation exists at the remote position from the reaction site of an olefin, the selectivities depend much on the reaction conditions due to the competitive intermolecular reactions of the uncoordinated carbenoids. Since zinc carbenoids produced by those procedures are mixtures of a variety of species having varying reactivities[4] and the proportion of the active species is changing during the reaction, controlling of the reaction species is vital to achieve high selectivity of the reaction. Especially in the cases of remote hydroxy-directed cyclopropanations of entropically unfavorable quasi-intramolecular process, the intermolecular reactions proceed easily and controlling of the reaction species becomes critical. Although several modified Furukawa procedures have recently been disclosed to improve activity of zinc carbenoids to unfunctionalized olefins,[5] stereoselective cyclopropanation by the remote hydroxy direction has not been studied well. Charret and coworkers[6] reported that the Furukawa procedure for allylic alcohols can be activated by a Lewis acid, but the effectiveness of this method for homoallylic or other remote olefinic alcohols is unknown. Stereoselective zinc carbenoid addition to **1** shown in Scheme 1 is an example of the entropically unfavorable hydroxy-directed reaction, where an olefin of the reaction site is separated by five bonds from the hydroxy group.[7] Stereoselectivity of the reaction is sensitive to the reaction conditions, and the product yield is easily reduced under inadequate conditions due to conversion of **1** to the corresponding acetal.[8] In this study, effects of reaction conditions on the stereoselectivity and the yield of the products **2** and **3** in the carbenoid reaction of **1** were carefully analyzed, and the dramatic improvements could be achieved based on these analyses.[9]

2. Results and discussions

2.1. Relation between the selectivity and the conversion

Stereoselectivity of cyclopropanation of **1** by the Furukawa procedure largely depends on the solvent employed.[8] The reactions in some ethers give high diastereomeric excess of



Scheme 1.

Keywords: asymmetric synthesis; zinc carbenoid; cyclopropanation; stereocontrol.

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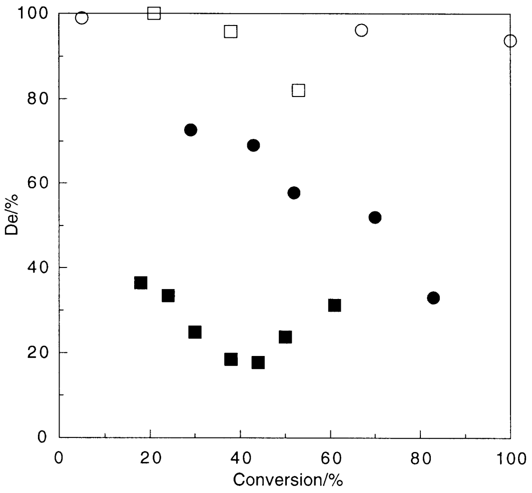

Figure 1. Diastereomeric excess of **2** and **3** as a function of conversion of **1** during the reaction in DME with the reagents at the ratio (diethylzinc/diiodomethane) of 5/10 (○), and in diethyl ether at 5/10 (●), at 5/5 (□), and at 5/2 (■) according to the Furukawa procedure.

the products **2** and **3**; 94% de in THF, 94% de in dioxane, and 95% de in DME at room temperature (%de = 100(**2** − **3**)/(**2** + **3**)). The yields under these conditions are moderate in a range of 56–65% even with the excess reagents; 5 equiv. of diethylzinc and 10 equiv. of diiodomethane (abbreviated as 5/10). On the other hand, use of non-ethereal solvent lowers the de to 41% (hexane), 49% (benzene), and 14% (dichloromethane). Surprisingly, the selectivity in diethyl ether becomes lowest and even reversed (−8% de, 73% yield). The present study started with observation of this anomalous solvent dependency.

When the reactions were interrupted before the completion of reaction, the de was found to change with conversion. The de vs. conversion relationships shown in Fig. 1 are different depending on the solvent and amounts of the reagents. In DME, the de was kept high during the reaction under the 5/10 conditions, and the de was still higher at lower conversions; e.g. 99% de at 5% conversion. In diethyl ether, the de decreases toward zero as the reaction proceeds under the same 5/10 conditions. This experiment suggests that the de in diethyl ether is high with a specific reaction species formed in the early stage of reaction. The high de of over 99% was in fact observed under the 5/5 conditions in diethyl ether at 21% conversion. In contrast, the use of a less amount of diiodomethane (5/2 conditions) resulted in an unexplainable change of the de that remains low throughout the reaction.

These results indicate that there are at least two reaction species to give the opposite stereoselectivity. So, if one desirable species can be effectively generated, the high de as well as the high product yield may be achieved.

2.2. Modifications of the Furukawa procedure

During the reaction according to the Furukawa procedure, the reaction species changes in two ways; formation of the zinc carbenoid and its consumption or decomposition. To separate these two factors, we first investigated the reaction with pre-formed carbenoid reagents. By mixing a 1/1 molar ratio of diethylzinc and diiodomethane, a species expressed as $EtZnCH_2I$ is expected to be produced, and the 1/2 mixture gives $Zn(CH_2I)_2$. The reactions were carried out by adding the pre-formed carbenoid to a solution of **1**. Results of the reactions in diethyl ether, THF, and DME are summarized in Table 1.

All the values of de given in entries 1–6 are as high as 93–96%, and the low value of the de in diethyl ether by the original Furukawa procedure was dramatically improved. The solvent dependency of the de was thus solved, and the formation process of the carbenoid was found to be important. Although the high de was achieved in all ethereal solvents, the product yields are not satisfactory even with 5 equiv. of the carbenoid species. We assumed that this is due to the decomposition of the carbenoids after their formation.[10] As the chemical yields are always high with the 1/1 mixture, $EtZnCH_2I$ seems to be more stable than $Zn(CH_2I)_2$. When the pre-formed $EtZnCH_2I$ was added dropwise until the substrate was consumed, the de or the chemical yield was not improved, but amounts of the reagents could be reduced in diethyl ether (entries 7–9).

To achieve the high chemical yield while maintaining the high de, decomposition of the active carbenoid should be minimized, because it provides other zinc species, which may result in a change in the coordination mode of the zinc carbenoid and in turn decomposition of **1**. Our final modification of the Furukawa procedure is a slow addition of diiodomethane to a mixture of diethylzinc and **1**. The reaction was monitored by TLC and the addition of diiodomethane was stopped at the consumption of **1** when the

Table 1. De and yield of the product in the reaction of pre-formed carbenoids

Entry	Solvent	Et_2Zn (equiv.)	CH_2I_2 (equiv.)	Reaction time (h)[a]	Addition time (h)[b]	de (%)	Yield (%)
1	OEt_2	5	10	1.5	–	95	59.5
2	OEt_2	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
7	OEt_2	2	2	–	0.5	96	31.6
8	OEt_2	3	3	–	1.0	97	53.6
9	OEt_2	2	2	–	2.0	97	51.3
10	THF	4	4	–	18.0	96	36.3

[a] The pre-formed carbenoid was added within a few minutes and stirring was continued during the reaction time.
[b] The pre-formed carbenoid was added dropwise during the addition time.

Table 2. The product yields and de's obtained by the slow addition of diiodomethane

Entry	Solvent	Et_2Zn (equiv.)	CH_2I_2 (equiv.)	Addition time (h)	de (%)	Yield (%)
1	OEt_2	4	3	6.5	96	92.4
2	OEt_2	2	1	1.0	97	61.5
3	OEt_2	1	1–2	1.0–2.0	–	0
4	DME	4	3	3.5	94	63.6
5	THF	2	1–3	1.0–3.0	–	0
6	Hexane	4	3	4.5	86	55.1
7	Hexane	2	1	1.0	81	75.1
8	Hexane	1	1	1.0	–	0
9	CH_2Cl_2	4	3	2.0	–	0

cycloaddition occurred. The results are summarized in Table 2.

Contrasting solvent effects were observed in this procedure. Although none of the products were obtained in dichloromethane or THF, moderate yields of the products were attained even with minimum amounts of diethylzinc (2 equiv.) and diiodomethane (1 equiv.) in diethyl ether and hexane (entries 2 and 7). The best results in terms of de and yield were achieved by using somewhat more but still reasonable amounts of the reagents in diethyl ether: 96% de and 92% yield as in the case of entry 1. The solvent dependency on the yield with the minimum reagents indicates that zinc carbenoid produced by this method reacts highly selectively but is not active enough in a polar solvent, THF.

2.3. Active species for the hydroxy-directed cyclopropanation

The success in the minimization of the reagents for the stereoselective addition prompted us to characterize the reaction species in the quasi-intramolecular addition. A minimum unit of the species is expected to consist of two organozinc and one methylene group. When **1** was added to a 1/1 mixture of diethylzinc and diiodomethane in diethyl ether, the reaction did not occur at all but addition of another equivalent of diethylzinc to this mixture promoted the reaction to give 41.4% yield of the product in 96% de. Another experiment was carried out by starting with reaction of **1** with sodium hydride and then adding zinc iodide to give a species like ROZnI. To this mixture, 1 equiv. each of diethylzinc and diiodomethane were added to result in 45.6% yield of the product of 96% de. These experiments support that the above minimum required unit is essential of the quasi-intramolecular addition. The active species in the present system can be represented as shown in Fig. 2.[11]

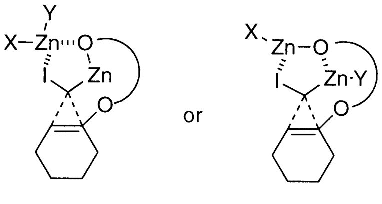

Figure 2. Possible structures of active species for the intramolecular carbenoid reaction.

2.4. Cyclopropanation of hydroxy-protected 1

The reaction selectivity of **1** in diethyl ether under the original Furukawa conditions shown in Fig. 1 indicates that, in the later stage, the selectivity is reversed and **3** is produced as a major product. In this stage, the quasi-intramolecular reaction species might be deactivated and intermolecular reaction to produce **3** may show up. The selectivity of the intermolecular reaction is studied with two analogous substrates, **4** and **5**, where the hydroxy group of **1** was protected with acetyl and *t*-butyldimethylsilyl groups, respectively. The reaction was carried out under the Furukawa and the Simmons–Smith conditions. The results are shown in Table 3. The results with dichlorocarbene are also given for comparison.

The reactions of the acetyl-protected substrate **4** (entries 1–6) again showed a characteristic change among the solvents employed. Higher values of the de in non-polar solvents may suggest occurrence of a weak interaction between the acetyl group and zinc carbenoid. The reversal of the de was observed in THF (entries 4 and 6), but the degree is lower than values expected from the results shown in Fig. 1. The high de in the opposite direction was observed with the TBS-protected **5** up to -77% (in hexane, entry 7). With this substrate, the reaction did not proceed at all in ethereal solvents by either of the methods, and the reactant **5** was recovered quantitatively. The stereochemical switching by the TBS protection was also observed in the reaction with dichlorocarbene, which is expected to be weakly directed by the hydroxy group.[12]

The selectivity switching due to the hydroxy group protection was experimentally demonstrated with the Furukawa procedure. However, the de dependency in the reaction of **5** on the solvent is not the same as that in the later stage of the reaction of **1**. This may exhibit an additional role of zinc incorporated in **1**: a deactivated zinc species placed at the hydroxy group has an ability to coordinate to the vinylic ether oxygen to fix the conformation of the pentanediol tether.

3. Conclusion

The slight modification of the Furukawa procedure improved cyclopropanation of **1** to give the high de irrespective of the solvent used. This improvement makes possible to apply the present stereoselective reaction to syntheses of optically active compounds irrespective of the solubility and

Table 3. Reactions of hydroxy-protected substrates **4** and **5**

Entry	Substrate	Conditions[a]	Solvent	Temperature (°C)	Time (h)	de (%)	Yield (%)
1	**4**	F	Hexane	0	1.5	75	80.1
2	**4**	F	CH_2Cl_2	0	1	86	89.8
3	**4**	F	OEt_2	0	4	47	21.0
4	**4**	F	THF	20	65	−18	29.8
5	**4**	SS	OEt_2	40	2.5	36	38.4
6	**4**	SS	THF	60	4.5	−11	18.1
7	**5**	F	Hexane	20	20	−77	20.7
8	**5**	F	CH_2Cl_2	0	1	−35	69.5
9	**5**	F	OEt_2	20	15	–	0
10	**5**	F	THF	20	15	–	0
11	**5**	SS	OEt_2	40	7.5	–	0
12	**5**	SS	THF	60	50	−25	12.0
13	**1**	**:**CCl_2	$CHCl_3$	0	1	16	43.0
14	**5**	**:**CCl_2	$CHCl_3$	0	1	−46	97.0
15	**5**	**:**CCl_2	Hexane[b]	0	2	−35	34.2

[a] F: The Furukawa procedure with 5 equiv. of Et_2Zn and 10 equiv. of CH_2I_2. SS: The Simmons–Smith reaction with 3 equiv. each of Zn/Cu and CH_2I_2. **:**CCl_2: Reaction of dichlorocarbene generated from $CHCl_3$ and NaOH/Bu_4NCl in $CHCl_3$.

[b] 10% (w/w) of $CHCl_3$ in hexane.

reactivity of the substrate as well as incorporation of additional ethereal functionalities in the substrate. We also found the minimum unit of the hydroxy-directed species, which was not found during study of the common entropically favorable systems. In those cases, formation of various carbenoids does not affect much the results due to the quick addition of the hydroxy-directed species. Coordination or reaction of the hydroxy group donates electrons to the zinc atom to reduce the electrophilicity of the zinc carbenoid, which retards the cyclopropanation. The present results reasonably explain how to re-activate the carbenoid to minimize the intermolecular side reaction. The present study also indicates that survey of the reaction solvent is important to find optimized conditions when a hydroxy group to direct zinc carbenoid is at a remote position of the reaction site.

4. Experimental

4.1. General

All temperatures are uncorrected. ^1H NMR (400 MHz) spectra were recorded on a JEOL GX-400 spectrometer in $CDCl_3$ or C_6D_6 using residual solvent peak as an internal standard (7.24 or 7.10 ppm). Analytical GLC of products **2** and **3** was conducted by the reported method[8] with a capillary column (PEG-20M, 0.25 mm i.d. 50 m). Diethylzinc was purchased from Kanto Kagaku Co. as a hexane solution (1.04 M). All solvents were purified by distillation in the presence of a proper dehydrating agent. All reactions were carried out under a dry nitrogen atmosphere.

4.2. Cyclopropanation of 1 resulting in high yield and high de (entry 1 in Table 2)

To a solution of **1** (169.1 mg) in dry diethyl ether (30 ml), a hexane solution of diethyl zinc (3.7 ml) was added at room temperature (20°C). To this mixture, a solution of diiodomethane (0.24 ml) in diethyl ether (60 ml) was added dropwise in 6.5 h. The resulting mixture was poured into a saturated aqueous solution of ammonium chloride. A regular workup and silica gel chromatography (elution with 20% ethyl acetate in hexane) gave a colorless oil (168 mg, 92.4% yield).

4.2.1. Preparation of 4. A mixture of **1** (498 mg, 2.71 mmol) and acetic anhydride (0.8 ml, 8.48 mmol) in anhydrous pyridine (2 ml) was stirred for 3 h at room temperature. After addition of water, the mixture was extracted with diethyl ether (20 ml×2) and washed with saturated aqueous copper sulfate (20 ml×4). The organic layer was dried over magnesium sulfate, concentrated, and purified by silica gel column chromatography (elution with 20% ethyl acetate in hexane) to give 390 mg of a colorless oil (63.7% yield). $[\alpha]^{D}_{20}=-42.8$ (*c* 1.1, methanol), IR (neat, KCl) 2980, 2940, 2850, 1740, 1670, 1380, 1240, 1180 cm^{-1}; ^1H NMR ($CDCl_3$) 5.12 (m, 1H), 4.59 (m, 1H), 4.12 (m, 1H), 2.06–1.92 (m, 4H), 2.00 (s, 3H), 1.79–1.48 (m, 6H), 1.23 (d, *J*=6.4 Hz, 3H), 1.19 (d, *J*=6.4 Hz, 3H); Anal. Found: C, 69.04; H, 9.51. Calcd for $C_{13}H_{22}O_3$: C, 69.30; H, 9.40.

4.2.2. Preparation of 5. To a mixture of *t*-butyldimethylsilyl chloride (2.40 g, 15.9 mmol), imidazole (2.44 g, 35.8 mmol), and a catalytic amount of 4-dimethylaminopyridine in DMF (20 ml), **1** (1.65 g, 8.97 mmol) was added in 5 min at room temperature. After stirring for 30 min, the mixture was poured into a saturated aqueous sodium bicarbonate solution (50 ml) and extracted with diethyl ether (80 ml×3). The organic layer was dried over sodium sulfate and concentrated to give a yellow oil (4.21 g), which was purified by silica gel column chromatography (elution with 2% ethyl acetate in hexane) to afford 2.58 g of a colorless oil (96.0% yield). $[\alpha]^{D}_{20}=-59.8$ (*c* 0.9, methanol), IR (neat, KCl) 2925, 2850, 1670, 1370, 1250, 1180, 1060, 840, 770 cm^{-1}; ^1H NMR (C_6D_6) 4.72 (m, 1H), 4.41 (m, 1H), 4.36 (m, 1H), 4.20 (m, 1H), 2.20 (m, 1H), 2.11 (m, 1H), 1.75–1.52 (m, 6H), 1.20 (d, *J*=6.1 Hz, 3H), 1.13 (d, *J*=6.1 Hz, 3H), 1.06 (s, 9H), 1.00–0.98 (m, 2H), 0.17–0.14 (m, 6H); Anal. Found: C, 68.29; H, 11.38. Calcd for $C_{17}H_{34}O_2Si$: C, 68.39; H, 11.48.

4.3. Dichlorocarbene addition to 1

To a solution of **1** (93 mg, 0.51 mmol) and triethylbenzylammonium chloride (36 mg, 0.15 mmol) in chloroform (5 ml) was added an aqueous solution of sodium hydroxide (50%, 4 g) in 15 min at 0°C. The mixture was allowed to stand for 30 min at the same temperature, and was extracted with dichloromethane (10 ml×4) after addition of water (10 ml). The organic layer was dried over sodium sulfate, and then concentrated to give 161 mg of a yellow oil. This was purified by silica gel column chromatography (elution with 10% ethyl ether in benzene) to give 57.5 mg of a colorless oil (a mixture of the diastereomers, 42.7% yield). The isomeric ratio of this mixture was determined by the capillary GLC analysis after dehalogenation. Dehalogenation was carried out with sodium in a mixture of diethyl ether, methanol, and water at 0°C to give a mixture of **2** and **3**.

4.3.1. Dichlorocarbene addition to 5. The substrate **5** was treated in the same way as **1**. In this case, the two isomers were separated by silica gel column chromatography (elution with 1% ethyl acetate in hexane). The minor isomer (the same stereochemistry as **2**) was obtained in 19.3% yield: $[\alpha]^{D}_{20}=-38.9$ (*c* 1.0, methanol); IR (neat, KCl) 2950, 2850, 1200, 840, 780 cm^{-1}; ^{1}H NMR ($CDCl_3$) 4.02–3.91 (m, 2H), 2.18–1.98 (m, 3H), 1.68 (m, 1H), 1.62 (m, 1H), 1,55–1.49 (m, 2H), 1.46–1.32 (m, 4H), 1.25 (d, J=6.3 Hz, 3H), 1.12 (d, J=6.1 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H). MS Found: *m/z* 365.1448. Calcd for $C_{17}H_{31}Cl_2O_2Si$ ($M^{+}-CH_3$): 365.1470. The major isomer (the same stereochemistry as **3**) was obtained in 44.3% yield: $[\alpha]^{D}_{20}=-5.35$ (*c* 1.1, methanol); IR (neat, KCl) 2950, 2850, 1200, 840, 780 cm^{-1}; ^{1}H NMR ($CDCl_3$) 3.97–3.87 (m, 2H), 2.13–2.09 (m, 2H), 2.03 (m, 1H), 1.82–1.76 (m, 2H), 1.69–1.58 (m, 2H), 1.47–1.36 (m, 3H), 1.27 (m, 1H), 1.20 (d, J=6.1 Hz, 3H), 1.15 (d, J=6.1 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H). MS Found: *m/z* 365.1458. Calcd for $C_{17}H_{31}Cl_2O_2Si$ ($M^{+}-Me$): 365.1470. To a solution of the major isomer (227 mg, 0.71 mmol) in diethyl ether (28 ml) was added a small piece of sodium (ca. 100 mg) at 0°C. To this solution, a mixture of methanol and water (100/3.3) was added dropwise. The additions of sodium and methanol–water were repeated until the reactant was not detected on a TLC analysis. The mixture was concentrated in vacuo, extracted with diethyl ether (100 ml×3) after addition of water (100 ml), washed with a saturated aqueous sodium chloride solution, and dried over sodium sulfate. Desilylation of the obtained mixture by the treatment with tetrabutylammonium fluoride in a mixture of THF and triethylamine (2/1) and purification by silica gel column chromatography (elution with 15% ethyl acetate in hexane) afforded diastereomerically pure **3** (112 mg, 79.9%). *Compound* **3**: $[\alpha]^{D}_{20}=-69.0$ (*c* 1.0, methanol); IR (neat, KCl) 3450, 2975, 2950, 2875 cm^{-1}; ^{1}H NMR ($CDCl_3$) 4.03–3.96 (m, 2H), 2.85 (broad s, 1H), 2.10–1.91 (m, 3H), 1.64 (broad s, 1H), 1.60–1.39 (m, 5H), 1.23–1.22 (d, J=6.4 Hz, 3H), 1.16–1.14 (d, J=6.4 Hz, 3H), 1.26–1.15 (m, 2H), 0.92 (ddm, J=10.7, 5.4 Hz, 1H), 0.26 (dd, J=6.3, 5.4 Hz, 1H); MS Found: *m/z* 198.1611. Calcd for $C_{12}H_{22}O_2$: 198.1614. The diastereomeric excess of the product from the dihalocarbene addition to **5** was determined by the GLC analysis after converting the adduct to a mixture of **2** and **3** by the same procedure without purification.

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