Stereoselective Intramolecular O–H Insertion of Rhodium Carbenoid Controlled by the 2,4-Pentanediol Tether

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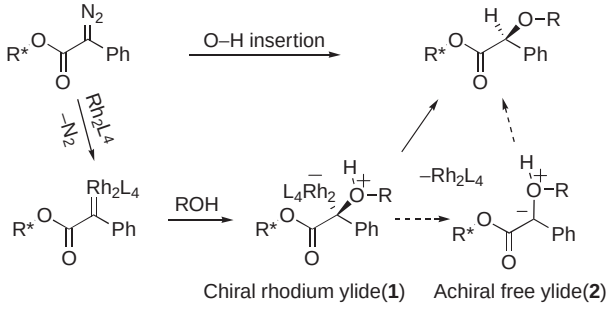
(Received July 8, 2005; CL-050885)

Intramolecular O–H insertion of acetodiazoacetate esters gave cyclic ethers of up to 86% diastereomer excess when 2,4-pentanediol was employed as a chiral tether. The selectivity of the reaction was suggested to be determined at the later stage of the reaction after dissociation of the catalyst.

A diazo compound reacts with an alcoholic function in the presence of a proper catalyst to result in the O–H insertion, which is considered to be an effective method for the formation of ethereal functions.[1] Since an achiral diazo carbon transforms to a chiral ethereal α-carbon during the reaction, stereocontrol of this reaction provides a useful asymmetric synthesis. However, only a few examples were reported for this issue. For the reaction of phenyldiazoacetate or (*E*)-styryldiazoacetate esters derived from chiral alcohols, the stereochemical purity of the product was moderate up to 53% diastereomer excess (de) with a achiral rhodium catalyst[2] and 70% de with an chiral catalyst having a matched configuration.[3] The diastereoselective O–H insertion starts with generation of the rhodium carbenoid. The succeeding stereodirected addition to an alcohol (or water) gives a chiral rhodium-associated ylide (**1**), the stereochemistry of which should carry over in retention to the final product (Scheme 1). However, the low de of the product compared with the stereocontrollability of the chiral auxiliary (R*) in the initial addition suggested that the rhodium dissociation/proton transfer process is not fully stereospecific or part of the rhodium ylide is converted to an achiral metal-free ylide (**2**) to give a stereoisomeric mixture.

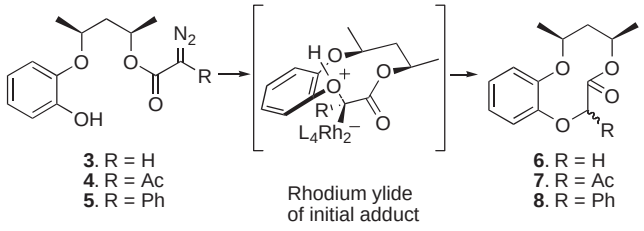


Scheme 1.

The 2,4-pentanediol (PD) tether is a promising stereocontroller applicable to diverse reactions, where the stereochemistry of the intramolecular reaction is strictly controlled.[4] The PD tether also controls a reaction of the cyclic intermediate generated by the internal addition.[5] Hence, the PD tether was expected to control the O–H insertion both in the initial addition and in the succeeding proton transfer.[6]

The substrates **3**–**5** carrying different diazo groups were prepared from stereochemically pure (*R*,*R*)-2,4-pentanediol.[7] On addition of $Rh_2(OCOCF_3)_4$ (5 mol %) in dichloromethane, **3** and **5** were consumed smoothly at rt, but the reaction of **4** needed some higher temperature. The yields of the cyclic ethers **6**–**8** obtained were 100% from **3**, 76% from **4** (at 50 °C), while 0% from **5**. Inefficient intramolecular reaction with **5** to give **8** is attributable to the steric repulsion between the two aromatic groups at the initial adduct shown in Scheme 2.[8] Since the reaction of **3** does not generate a new stereogenic center, we selected acetodiazoacetate as a source of the carbenoid, and stereoselectivities of the O–H insertion with **4** and the related substrates **9**–**11** shown Figure 1 were studied.

When **4** was treated with $Rh_2(OCOC_3F_7)_4$ (5 mol %), a more reactive analogue of $Rh_2(OCOCF_3)_4$, the cyclic products **7** was obtained almost quantitatively at rt, while the same reactions with **9**–**11** involved some side-reactions to give the cyclic ethers **12**–**14** in 42–55% isolation yield. All the cyclic ethers consisted of pairs of the diastereomers, but the enol isomers were not detected by the ^1H NMR in $CDCl_3$. The de values determined by the NMR are given in Table 1, and were found to be insensitive to the catalyst employed; the same de values were obtained with $Rh_2(OCOCF_3)_4$ in dichloromethane at rt or in benzene at 50 °C. The reaction with $Rh_2(OAc)_4$ was sluggish even at 50 °C, but the



Scheme 2.

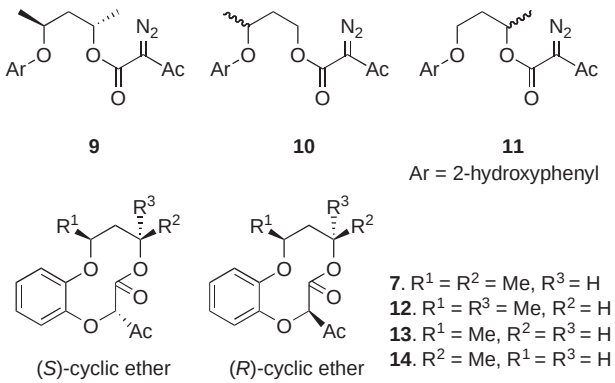


Figure 1. Structures of the substrates **9**–**11** and the O–H insertion products **7** and **12**–**14**.

Table 1. Stereoselectivity and the best yield of the O–H insertion reaction with **4** and **9**–**11**, and the de of **7** and **12**–**14** in equilibrium (catalyzed by DABCO)

Substrate	Product (the best yield)	De of insertion	De in equilibrium
4	**7** (76%)	86%	86%
9	**12** (46%)	68%	66%
10	**13** (54%)	80%	80%
11	**14** (42%)	20%	18%

de obtained were still the same. So far, the PD tether of **4** having heterochiralities was found to be the best chiral tether to result in 86% de.

Stereochemically pure **7** and **12** (>99% de) were obtained by a single recrystallization of the diastereomeric mixtures, and the stereochemistries of the major isomer at the α-position were determined to be *R* for the both compounds by the X-ray analyses as shown in Figure 2.[9] The α-proton is placed close to the aromatic ring, and the acetyl group sticks out.

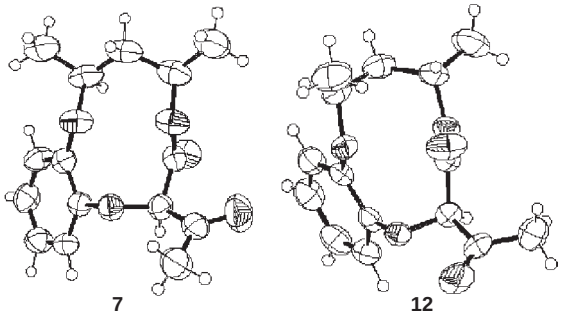


Figure 2. ORTEP drawings of **7** and **12**.

The stereochemistry of (*R*)-**7** indicates that the O–H insertion with **4** does not proceed via the concerted and stereo-retention rhodium/hydrogen replacement at the initial adduct given in Scheme 2. Since the stereoselectivity was insensitive to the ligands of the rhodium catalysts, the rhodium metal should be dissociated prior to the generation of the chirality by the proton transfer. This mechanism is different from that reported for the asymmetric O–H insertions using the phenyl- or styryldiazoacetate,[2,3,10] but is reasonable because of the acetoacetate structure of **4** stabilizing negative charge developed by the dissociation of the rhodium catalyst. In such a reaction process, the chirality generated by the carbenoid addition to the O–H function disappears once, and then, the isomerization of the resulting metal-free ylide needs to be stereo-differentiated. The stereocontrol of such a reaction on a cyclic compound consisting of PD is possible as deduced from the strict stereocontrol observed in the hydrogen addition to a 10-membered ring radical intermediate.[5]

In the last part of this report, we will present evidence that the stereogenic center is established during the insertion reaction, but not after the reaction. The de values were changed by the treatment with excess *t*-BuOK in *t*-BuOH at 30 °C and by the following quench with aqueous NH_4Cl. The results of the isomerization largely depended on the quenching conditions; e.g., between 48% and −40% in the case of **7**. Base-catalyzed isomerization in $CDCl_3$ reached immediately the equilibrium by the addition of DABCO (3% v/v) at rt. The de values in equilibrium given in the last column of Table 1 are very similar to those obtained by the O–H insertion in all four substrates.

These results seem to indicate that the isomerization occurs during the operation of the O–H insertion reaction, but it was clearly excluded by the following experiments. The isomerization did occur by the addition of acetic acid (3% v/v) in $CDCl_3$ at rt ($t_{1/2} = 12$ h), but this is too slow to govern the stereochemistry of the O–H insertion reaction. The addition of $Rh_2(OCOC_3F_7)_4$ did not cause any isomerization at rt for 24 h. Further, the O–H insertion reaction of **9** to give **12** was carried out in the presence of stereochemically pure **7**, which was recovered unchanged as the same stereochemically pure form.

In the present report, it is shown that the PD-tethered reaction is effective to perform the stereocontrolled O–H insertion reaction with the acetodiazoacetate esters. The stereocontrol factor is apparently different from that with the other diazo esters, and the stereoselectivity must be controlled at the later stage of the reaction, the proton transfer step.

The authors would like to express their thanks to Dr. Hiroki Akutsu of University of Hyogo for the X-ray analyses. This work was supported by a Grant-in-Aid for Scientific Research (B) No. 16350026 from the Japan Society for the Promotion of Science (JSPS).

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7 A common precursor for **3**–**5** was prepared in a stereochemically pure form by the Mitsunobu reaction of (*R*,*R*)-2,4-pentanediol and 2-*t*-butyldimethylsilyloxyphenol in 71% yield. Desilylation was achieved in a quantitative yield before or after the manipulation at the remaining hydroxy group to introduce the diazo esters. The substrate **9** was prepared through an additional Mitsunobu reaction with benzoic acid. **10** and **11** were prepared with 3-hydroxybutyl benzoate and 1,3-butanediol, respectively, in a similar way.
8 The conformation of the initial adduct was illustrated based on the results with the related PD-tethered reactions. See: T. Sugimura, K. Hagiya, Y. Sato, T. Tei, A. Tai, and T. Okuyama, *Org. Lett.*, **3**, 37 (2001).
9 Crystal data of **7**: $C_{30}H_{36}O_{10}$, $M_r = 556.61$, orthorhombic, $P2_1/n$, $a = 8.9016(7)$, $b = 11.8711(10)$, $c = 27.806(2)$ Å, $V = 2938.3(4)$ Å^3, $Z = 4$, $D_{calcd} = 1.26$ g cm^{-3}, R (R_w) = 0.062 (0.054) for 3612 reflections with $I > 2.0\sigma(I)$. **12**: $C_{15}H_{18}O_5$, $M_r = 278.30$, orthorhombic, $P2_1/n$, $a = 9.581(4)$, $b = 9.5266(9)$, $c = 16.2213(17)$ Å, $V = 1480.6(7)$ Å^3, $Z = 4$, $D_{calcd} = 1.25$ g cm^{-3}, R (R_w) = 0.070(0.066) for 2004 reflections with $I > 2.0\sigma(I)$. Crystallographic data reported in this manuscript have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 281652 & 281653. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).
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Published on the web (Advance View) September 3, 2005; DOI 10.1246/cl.2005.1328