# Carbenoid Addition to Phenols to Give Cycloheptatrienols. Stereochemical Regulation and Ligand-dependent Switching of Chemoselectivity

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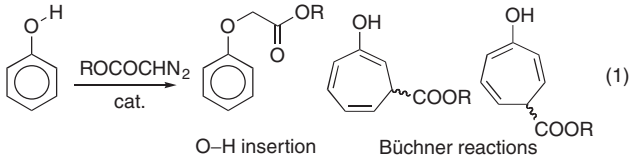
Cycloheptatrienols were prepared stereoselectively by the intramolecular Büchner reaction of phenols using a 2,4-pentanediol tether of suitable stereochemistry, where the intrinsically favorable O–H insertion is effectively suppressed.

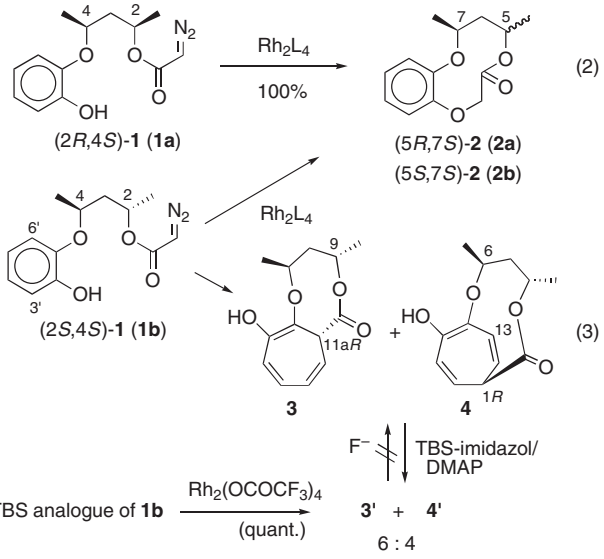
Metal carbenoid generated from a diazo compound is a useful species having both sufficient reactivity and reasonable selectivity with various functional groups.[1] Selectivity in the reaction with a multi-functionalized substrate depends on the structure of the diazo compound and the catalyst employed, but the reactivity of the functional group is more influential than the nature of the carbenoid.[2] The O–H insertion reaction is very fast, and usually preferred to other carbenoid reactions.[3] Phenol offers a typical example; only the O–H insertion proceeds, but the addition to the aromatic $\pi$-bond (Büchner reaction) or C–H insertion does not occur irrespective of the carbenoid structure, reaction conditions, or substituent on the phenyl ring (eq 1).[4–7]



(1)

During our study of asymmetric syntheses using 2,4-pentanediol as a chiral tether,[8] $Rh_2(OCOCF_3)_4$-catalyzed reaction of diazo compound (2*R*,4*S*)-**1** (**1a**) was found to give **2a** in a quantitative yield via the intramolecular O–H insertion, though this reaction does not generate any new chiral center (eq 2).[9] In contrast, the reaction of a diastereomeric substrate, (2*S*,4*S*)-**1** (**1b**) led to the novel Büchner reaction, overcoming the O–H insertion, to yield chiral cycloheptatrienols **3** and **4** stereoselectively (eq 3), which is detailed in this communication.

Stereochemically pure diazo compound **1b** was subjected to the $Rh_2(OCOCF_3)_4$-catalyzed reaction in chloroform-*d* at room temperature. The reaction mixture mostly consisted of three intramolecular products, as analyzed by $^1$H NMR at 600 MHz. The two major products were those of the Büchner reaction **3** and **4**, while the O–H insertion product **2b** was minor. The mixture was unchanged at least for 1 h at room temperature, but **2b** was the only isolable compound by a silica gel column. Stereochemistries of **3** and **4** were assigned to 11a*R* and 1*R*, respectively, by the NOE experiments (H-9 to H-11a, and H-6 to H-13). Throughout the study, no diastereomers of **3** or **4** were detected in any reactions (<2% of **3** or **4**). Thus, the Büchner reaction of **1b** is stereoselective to proceed at the 1′,6′- and 4′,5′-positions.



(2)

(3)

Structures of **3** and **4** were confirmed by using their TBS analogues. When the hydroxy group in **1b** was protected with TBS prior to the reaction, a mixture of two products, **3′** and **4′**, the TBS analogues of **3** and **4**, was obtained quantitatively in a ratio of 61:39. Although deprotection of **3′** and **4′** with TBAF did not give **3** or **4** leading solely to the decomposed products, the TBS protection of a mixture of **3** and **4** could lead to these TBS analogues that were identical to **3′** and **4′**.

Several other catalysts were employed for the reaction. The total yields and compositions of the intramolecular adducts **2**–**4** are summarized in Table 1. $Rh_2(OCOC_3F_7)_4$ generates a very reactive carbenoid due to the strongly electron-accepting ligands, and in fact, the reaction completed in a short time to give the internal adducts in good yields as was with $Rh_2(OCOCF_3)_4$. The O–H insertion product **2b** was obtained only in 6%, but the remaining major part was a mixture of the two Büchner products **3** and **4**. In contrast, the intramolecular reactions with less electrophilic catalysts were slow and intermolecular reaction

**Table 1.** Total yields of the internal adducts and their compositions in the reaction of **1b**[a]

| Catalyst | Yield /% | Composition/% | | |
|---|---|---|---|---|
| | | **2b** | **3** | **4** |
| $Rh_2(OCOC_3F_7)_4$ | 97 | 6 | 42 | 52 |
| $Rh_2(OCOCF_3)_4$ | 92 | 10 | 44 | 46 |
| $Rh_2(OAc)_4$ | 21 | 77 | 0 | 23 |
| $Rh_2(OCOC_7H_{15})_4$ | 14 | 63 | 0 | 37 |
| $Rh_2$[(5*S*)-MEPY]$_4$[b] | 50 | 100 | 0 | 0 |

[a]Determined by $^1$H NMR. [b]MEPY = methyl 2-oxopyrrolidine-5-carboxylate.

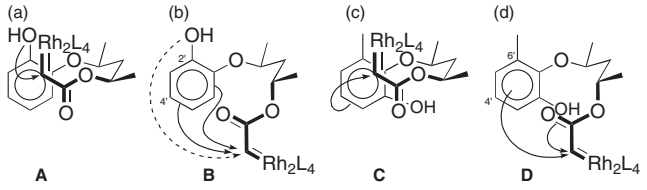
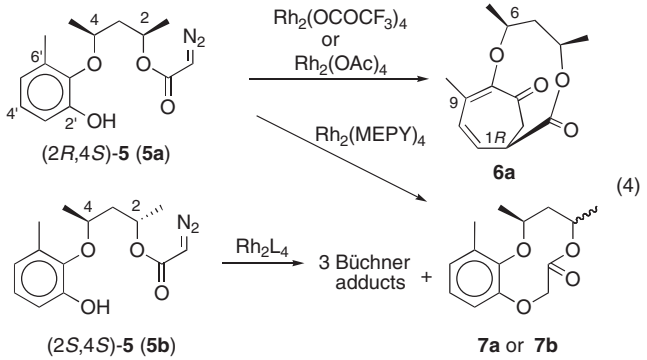



**Figure 1.** The most probable conformations of the carbenoids A, B, C, and D generated from **1a**, **1b**, **5a**, and **5b**, respectively.

with contaminated water became dominant. Among the intramolecular reactions, the O–H insertion to give **2b** was the major process and formation of **3** was not observed. A catalyst having carboxamidate ligands, $Rh_2(MEPY)_4$, resulted exclusively in the O–H insertion.[10] The reaction of **1a** was reinvestigated with varied catalysts, but the O–H insertion product **2a** was the only intramolecular adduct in any cases.

Formation of the Büchner products with **1b** is outstanding because the carbenoid part is accessible to the internal hydroxy group as demonstrated with the carboxamidate catalyst. The formation of **3** and **4** and their stereochemistries are explainable by the conformation of the carbenoids. The most probable conformers generated from **1a** and **1b** are illustrated in Figures 1a and 1b.[11] The geometries are flexible, but sufficiently regulated by chiralities on the tether. The face of the aromatic group to be added is determined by the orientation of the hydroxy group that sticks out to the less hindered space. The carbenoid part in A is close and easily accessible to the hydroxy group, while that in B is distant from it. When the carbenoid part in B is very reactive with perfluorocarboxylate ligands, it is intercepted by the aromatic $\pi$-electrons at closer 1′,6′- or 4′,5′-positions in place of the O–H insertion, while the interception becomes inefficient with the less reactive carbenoid carrying the carboxamidate. The switching mechanism between the OH and the Büchner reactions by the prearranged conformation of the carbenoids is confirmed by the reaction with 6′-methyl analogues **5a** and **5b**, where 6′-methyl group is bulkier than 2′-hydroxy group, and thus the methyl is placed at the outer position to bring the hydroxy inner as illustrated in Figures 1c and 1d.




As expected from the distant position of the hydroxy group in C, the reaction of **5a** carrying (2*R*,4*S*)-tether with $Rh_2(OCOCF_3)_4$ did not give any O–H insertion product **7a**, but afforded **6a** as a sole intramolecular product (eq 4). The yield of **6a** was only 14% owing to its instability under the reaction conditions. The yield became better 47%, without formation of **7a**, wen the catalyst was $Rh_2(OAc)_4$. The structural assignment of **6a** was based on the COSY spectra and the NOE between 6-Me and 9-Me. The structure determined is agreeable with the keto isomer of the Büchner product produced by the regio- and stereoselective addition at 3′,4′-position as shown in Figure 1c. Once again, the reaction with $Rh_2(MEPY)_4$ resulted only in the O–H insertion to give **7a** in 55% yield with some accompanying intermolecular side products. In the case of **5b** carrying (2*S*,4*S*)-tether, the carbenoid part placed closer position to the hydroxy group (Figure 1d). The reaction with $Rh_2(OCOCF_3)_4$ gave a mixture of **7b** and the Büchner products[12] in a ratio of 50:50 (61%). Use of $Rh_2(MEPY)_4$ catalyst changed the ratio to 97:3 (80%).

The present study disclosed that the chiral tether consisting of 2,4-pentanediol controls the reaction region to realize switching of the functional-group selectivity by the carbenoid ligand when the stereochemistry of the tether is proper. Stereoselective formation of cycloheptatrienols, **3** and **4**, is remarkable because it is difficult to achieve by other conventional methods due to the unstable enol structure.[13] The reaction control by the prearranged conformation of the reactant is one of characteristic features of the chiral tethered intramolecular reaction and may be governed by the principle of least motion.[14]

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