Hydroxy Direction of the Rhodium-mediated Dipolar Cycloaddition of Cyclic Carbenoids with Vinyl Ethers

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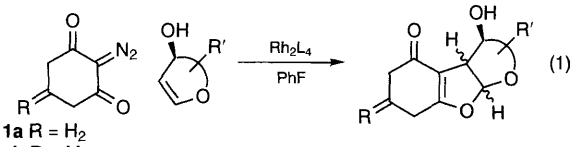
The dipolar cycloaddition of cyclic diazocarbonyl compounds with vinyl ethers is directed in a *syn* fashion by allylic hydroxy groups.

We have recently reported that the rhodium-mediated cycloaddition of cyclic diazodicarbonyl compounds with vinyl ethers and aromatic heterocycles is an effective route to polyheterocylic compounds.[1] We have also reported the use of chiral catalysts to engender asymmetry in this cycloaddition (reagent control).[2] In order to further examine the opportunities for stereochemical control in these processes, we have studied cycloadditions with enol ethers whose olefins are prochiral (substrate control). One example of a dipolar cycloaddition directed by an allylic hydroxy has previously been reported,[3] as has the use of metal chelation to direct such reactions.[4] This study was aimed at the simple question posed by eqn. (1): could

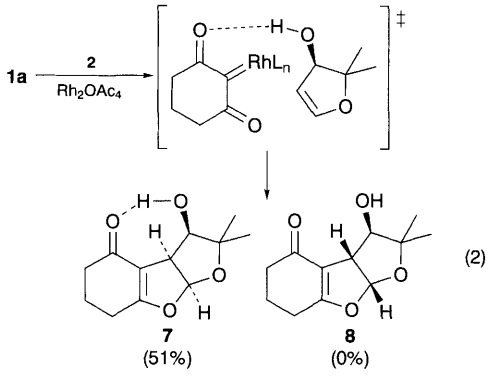


1a R = H_2
b R = Me_2
c R = H, CO_2Me

a hydroxy group direct cycloaddition in competition with O–H insertion,[5] the latter reaction being well-known among the many rhodium-mediated processes.

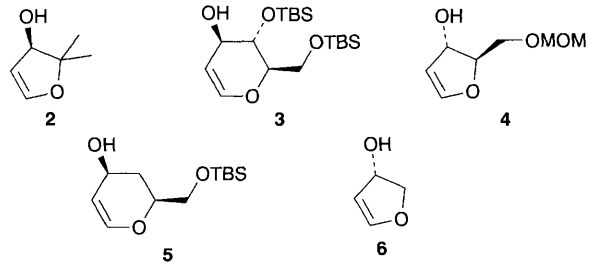
Glycals, available either from commercial sources or prepared by the Ireland method,[6] serve as readily accessible reactants with the desired substitution pattern. Five glycals were used in this preliminary study in reactions with three simple diazocompounds **1**. Compound **1c** was prepared from 3,4,5-trimethoxybenzoic acid in 4-steps (61%) (i, Li/NH_3; ii, MeOH, HCl; iii, H_2O, HCl; iv, MsN_3, Et_3N); the others are known. Compound **2** was obtained in three steps in an overall yield of 41% from erythronolactone acetonide as will be described in another publication;[7] it served as the prototype for mechanistic studies of the reaction. Compound **3** is readily available (58%) from triacetylglucal (i, NaOMe, MeOH; ii, TBSCl, imidazole; iii, BzCl, pyr; iv, TBSCl, imidazole; v, NaOMe, MeOH). Compound **4** was obtained (80%) from ribonolactone.[6] Compound **5** was obtained (28%) from triacetylglucal by Paquette's method.[8] Compound **6** was obtained in three steps from erythronolactone acetonide (i, DIBAL-H; ii, CCl_4, $P(NMe_2)_3$; iii, Li/NH_3).

It was envisioned that pre-equilibrium formation of a complex (either based on hydrogen-bonding of a carbonyl to the O–H group or Lewis acid–base interaction between the carbenoid carbon and the oxygen) could deliver the carbenoid to the *syn* face of the alkene in **2**. Exploratory reactions of **1a** with **2** (2–3 equiv.) were conducted in fluorobenzene, in which reactions of the highly reactive rhodium carbenoids derived from cyclohexanediones have been most successful. The rhodium acetate-mediated reaction produces a single diastereoisomeric product **7** in 51% yield, without a trace of its diastereoisomer **8**. Support for the structural assignment as the *endo* alcohol comes from physical methods [^{1}H NMR ($CDCl_3$): δ 6.18 (d, *J* 6.6, 1H), 4.20 (d, *J* 8.1, 1H), 3.94 (dd, *J* 8.1, 6.6, 1H), 2.50 (m, 2H), 2.43 (m, 2H), 2.09 (m, 2H), 1.32 (s, 3H), 1.18 (s, 3H); IR/cm^{-1} (thin film): 3392, 2949, 1623, 1426, 1407, 1381, 1316, 1235, 1185, 1118, 1084, 1060, 1006, 906, 815; EIMS *m/z*: 224, 206, 191, 163, 153, 137, 128, 98, 72, 57; HRMS *m/z* calcd. for $C_{12}H_{16}O_4$, 224.1049, found, 224.1055]. We have prepared a number of furo[2,3-*b*]furan derivatives related to **7** and **8**,[7] and find a key distinguishing feature is the absence of significant coupling between the carbinol proton and the bridgehead proton in compounds such as **8** with *exo* hydroxy stereochemistry; **7** shows a 8.1 Hz coupling between these protons. Compound **7** also shows a sharp, 3625 cm^{-1} OH absorption in dilute CCl_4 solution, strong evidence for an intramolecular hydrogen bond to the carbonyl. In the seven-membered ring involved here, this geometric arrangement could arise only with an alcohol on the concave face of the cupped ring system. Efforts to disrupt the idealized transition state depicted in eqn. (2) involved silylation



of the hydroxy group and a change of solvents. Stereoselectivity in cycloaddition to the TIPS-silylated glycal is 100% (48% isolated yield) but favours the *exo* stereochemistry, which was established by conversion of the major product to **8** (TBAF, THF). This datum supports the hypothesis that formed the basis for this study, namely that a hydroxy functionality could direct the metal-mediated dipolar cycloaddition in a *syn* fashion. Conducting the reaction in acetone, which would be expected to competitively hydrogen bond with the alcohol, produces a 2 : 1 mixture (49%) in favour of **7**. Cycloaddition in *tert*-butanol solvent gives **7** in both high stereoselectivity and 44% yield (surprisingly). Evidently, the carbenoids derived from **1** are reluctant to engage in O–H insertion processes.

These results encouraged the exploration of the generality of this principle with a number of other glycals. Fig. 1 shows the outcomes of several reactions between compounds **1** and **2–6**. The isolated yields are given below each product. In all cases,



only a single stereoisomer was detected. In several cases, cycloaddition to a TIPS-protected version of the alcohol has been performed, and the opposite stereochemistry has been obtained, as shown by deprotection.

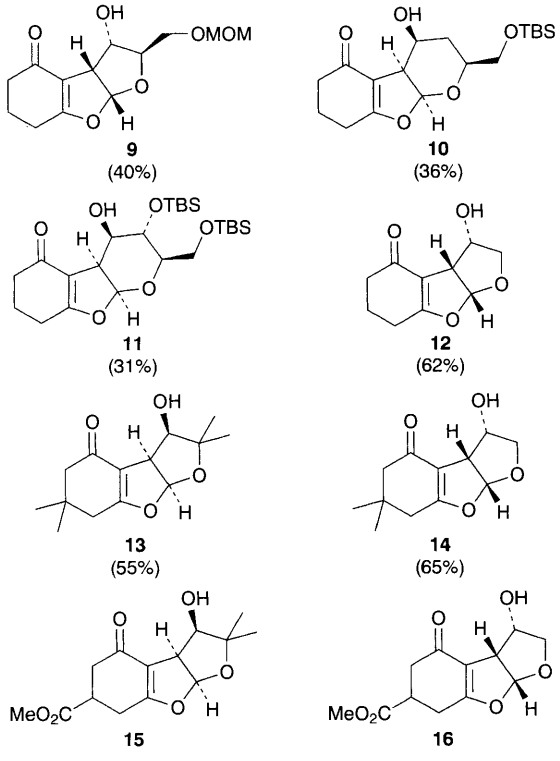


Fig. 1 Products from reactions between compounds **1** and **2–6**

Carbenoid additions directed by neighbouring hydroxy groups are among the oldest stereoselective reactions, the classic example being the Simmons–Smith cyclopropanation of cyclohexenol.[9] A wide variety of other directed reaction processes, including the Henbest and Sharpless hydroxy-directed epoxidations, are available for the control of stereochemistry in organic synthesis.[10] The examples provided in this work extend the principle to novel metals and novel transformations.

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