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Ligand-Dependent Site Selectivity in the Rh(II)-Catalyzed Decomposition of a Glycine-Derived Diazo Acetoacetamide

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Abstract: The product distribution obtained from the Rh(II)-catalyzed decomposition of α-diazoimide **1** can be selectively controlled by the proper choice of catalyst. While perfluorinated ligands favor isomünchnone formation, products derived from 6-ring cyclization are preferred using $Rh_2(OAc)_4$. The effect can be modulated by the addition $Sc(OTf)_3$ as a Lewis acid.
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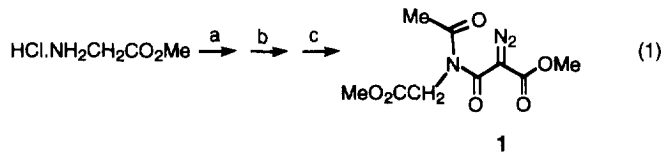
Metallo carbenoids derived from diazo compounds by transition metal-catalyzed decomposition reactions have attracted considerable attention in recent years as valuable intermediates for the efficient construction of structurally complex substrates from readily accessible precursors.[1] Rhodium(II) carboxylates and carboxamides have emerged as the catalysts of choice for chemo- and stereoselective diazo carbonyl reactions.[2] The resulting rhodium carbenoids can undergo a variety of synthetically valuable reactions including cyclopropanation,[3] X-H insertion (X = C, O, N)[4] or ylide formation by intramolecular ring-closure onto adjacent carbonyl groups.[5] For diazo compounds possessing several functional groups, the efficient and predictable control of chemoselectivity constitutes an important prerequisite for synthetic applications. Previous work in this area by several research groups clearly revealed the crucial role of molecular structure and nature of the catalyst for discriminating amongst the different reaction pathways.[6]

In view of our interest in the stereoselective applications of rhodium carbenoids, we have been investigating the Rh(II) catalyzed behavior of α-diazo carbonyl compounds derived from α-amino acid esters.[7] As an extension of our earlier studies, we prepared the achiral model substrate **1** in three steps and good overall yield from glycine methyl ester[8] (eq. 1) and studied its reactivity with various rhodium(II) catalysts (Scheme 1, Table 1).



(1)

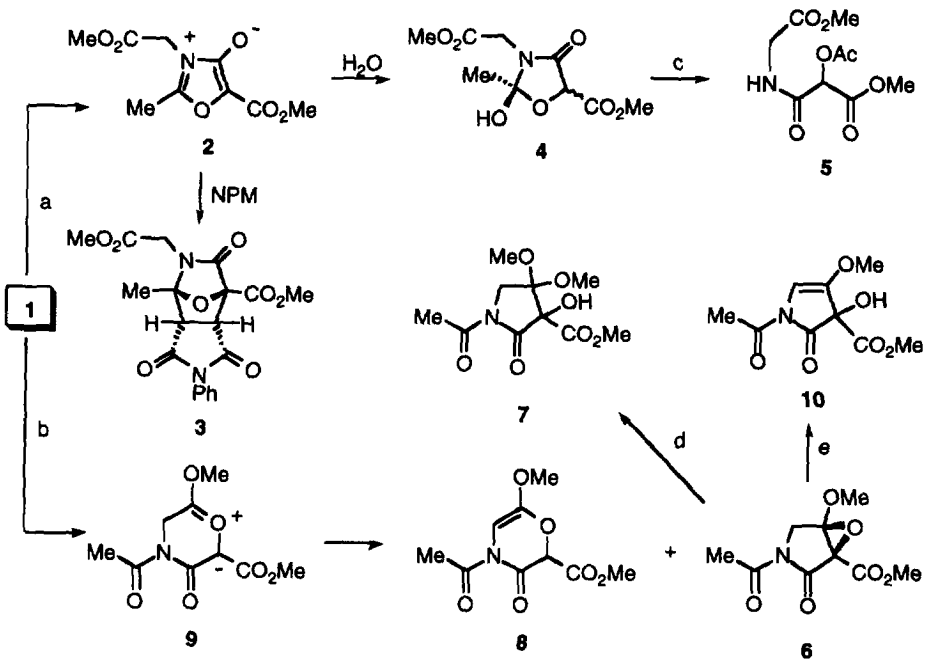
1

(a) AcCl, NEt_3; (b) $ClCOCH_2CO_2Me$, C_6H_6, Δ; (c) $CH_3SO_2N_3$, NEt_3 (69% overall)

In the presence of rhodium(II) perfluorobutyroamidate [$Rh_2(pfm)_4$] and using *N*-phenylmaleimide (NPM) as the dipolarophile, the *endo*-cycloadduct **3** was formed in 91 % yield (isolated) *via* 5-ring cyclization of the initially formed rhodium carbenoid onto the acetyl oxygen atom followed by a subsequent [3+2]-cycloaddition of the intermediate isomünchnone **2** (Table 1, entries 1,2).[9] A small amount (≤ 3 %) of the *exo*-isomer was also observed. When the reaction was carried out in $CDCl_3$ without any added dipolarophile, the smooth transformation of diazoimide **1** to the mesoionic dipole **2** could be monitored

directly by ^{1}H-NMR (entry 3). Although intermediate **2** was too labile for isolation, it could be trapped with N-phenyl maleimide to give cycloadduct **3**. Upon addition of water to the reaction mixture (entry 4), an equilibrium mixture of the diastereomers of hemiketal **4** formed, which rearranged to acetate **5** during column chromatography (84 % yield from **1**). Products derived from C-H insertion into the methylene group or 6-ring cyclization onto the ester carbonyl group were not observed.

Scheme I



Experimental Conditions: (a) $Rh_2(pfm)_4$; (b) $Rh_2(OAc)_4$; (c) SiO_2, 84 % from **1**; (d) MeOH, *p*-TsOH, rt, 14 h, 84 % from **1**; (e) $Sc(OTf)_3$, C_6H_6, reflux, 15 min, 74 % from **1**.

We next decided to test whether the observed preference for isomünchnone formation through 5-ring cyclization could be altered as a function of the nature of the ligand on the rhodium catalyst. While the fluorinated analogs (*i.e.* rhodium(II) perfluorobutyrate [$Rh_2(pfb)_4$] (entry 5) and rhodium(II) trifluoroacetate [$Rh_2(tfa)_4$] (entry 6)) both showed the same reactivity pattern as $Rh_2(pfm)_4$, the product distribution changed dramatically when rhodium(II) acetate [$Rh_2(OAc)_4$] was employed as the catalyst. In this case, only a small quantity of the isomünchnone cycloadduct **3** was observed when the reaction was carried out in refluxing benzene and in the presence of NPM (entry 7). The major product was epoxide **6**, produced by attack of the rhodium carbenoid on the ester carbonyl group. The epoxide proved to be too labile to isolate by column chromatography, however its structure was established by its characteristic ^{13}C-NMR signals (δ = 63.5 and 88.8 ppm) and *in situ* trapping with methanol to produce hydroxy acetal **7**. This compound could be isolated in 84 % yield (from **1**) and was fully characterized.[8] In addition, *ca* 3 % of enol ether **8** was also formed in the reaction mixture. A similar product distribution was encountered when the reaction was carried out in the presence of dimethyl acetylenedicarboxylate (DMAD), or without any

Table 1: Product distribution[a] in the Rh(II)-catalyzed decomposition of **1**

entry	catalyst[b]	conditions[c]	**2**	**3**	**4**	**6**	**8**
1	$Rh_2(pfm)_4$	A, NPM	-	95	-	-	-
2	$Rh_2(pfm)_4$	B, NPM	-	95	-	-	-
3	$Rh_2(pfm)_4$	C	90[d]	-	-	-	-
4	$Rh_2(pfm)_4$	B, H_2O	-	-	90	-	-
5	$Rh_2(pfb)_4$	A, NPM	-	95	-	-	-
6	$Rh_2(tfa)_4$	A, NPM	-	95	-	-	-
7	$Rh_2(OAc)_4$	A, NPM	-	3	-	90	3
8	$Rh_2(OAc)_4$	A, DMAD	-	-	-	90	3
9	$Rh_2(OAc)_4$	A	-	-	-	90	3
10	$Rh_2(cap)_4$	A, NPM	-	50	-	40	-
11	$Rh_2(OAc)_4$	A, NPM, $Sc(OTf)_3$	-	38[e]	-	-	-

(a) Yields determined by the integration of characteristic nmr signals of the crude product mixture, error limit ± 3 %; (b) pfm = perfluorobutyroamidate, pfb = perfluorobutyrate, tfa = trifluoroacetate, cap = caprolactamate; (c) A = benzene, reflux; B = methylene chloride, rt; C = $CDCl_3$, rt; (d) 20 % conversion of **1** after 1.5 h; (e) in addition, 26 % of acetate **5** was detected.

added dipolarophile (entries 8,9). While the enol ether **8** seems to stem from a proton shift from the 6-membered carbonyl ylide intermediate **9**,[10,11] it is not clear whether epoxide **6** is derived from charge collapse of the same intermediate or whether its formation is *via* a direct cyclopropanation of the ester C=O group by the rhodium carbenoid.

The above studies demonstrate that the reactivity of the transient rhodium carbenoid derived from α-diazoimide **1** is markedly dependent on the electronic nature of the rhodium catalyst with a distinct preference for isomünchnone formation from the fluorinated ligands. When rhodium caprolactamate [$Rh_2(cap)_4$] was used as the catalyst, roughly equal amounts of cycloadduct **3** and epoxide **6** were observed (entry 10). Interestingly, we were able to modulate the catalytic activity of $Rh_2(OAc)_4$ by the addition of $Sc(OTf)_3$ (10 mol %) as an external Lewis acid catalyst to the reaction mixture (entry 11). In this case, cycloadduct **3** and the rearranged water addition product **5** were obtained as the major products, while neither epoxide **6** nor the hydroxy enol ether **10** could be detected in the crude mixture. Structure **10** was formed (74 % isolated yield) in a control experiment involving the $Sc(OTf)_3$-catalyzed rearrangement of epoxide **6**. Apparently, the Lewis acid $Sc(OTf)_3$, which is known to strongly interact with carbonyl groups,[12] creates a more electrophilic carbenoid species and 5-ring cyclization prevails as in the electron-poor fluorinated ligand systems.

In summary, we have shown that the site of attack of a rhodium carbenoid onto adjacent carbonyl groups can be selectively controlled by the proper choice of catalyst and the presence of a Lewis acid.

At the present point in time, the mechanistic basis for this switch in reactivity is not fully understood. Although steric and conformational effects[13] may be involved, the variation of the electronic character of the transient rhodium carbenoid species also seems to be a contributing factor. Experiments to define the scope and generality of these concepts are presently underway in our laboratories.

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8. All unknown compounds in this study were fully characterized (IR, NMR, elemental analysis and/ or HRMS).
9. In a typical experiment, a mixture of the diazo compound (300 μmol), the Rh(II) catalyst (1 mg) and the dipolarophile (330 μmol) in 8 mL of benzene was heated at reflux until TLC indicated complete conversion of the starting imide **1** (ca. 1 h). The solvent was removed under reduced pressure and the product ratio was determined by quantitative NMR analysis.
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