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Rhodium (II) Catalyzed Intramolecular Dipolar Cycloaddition Reactions of Carbonyl Ylides. Computational and Empirical Studies of the Regio- and Chemoselective Effect of Catalyst Ligand

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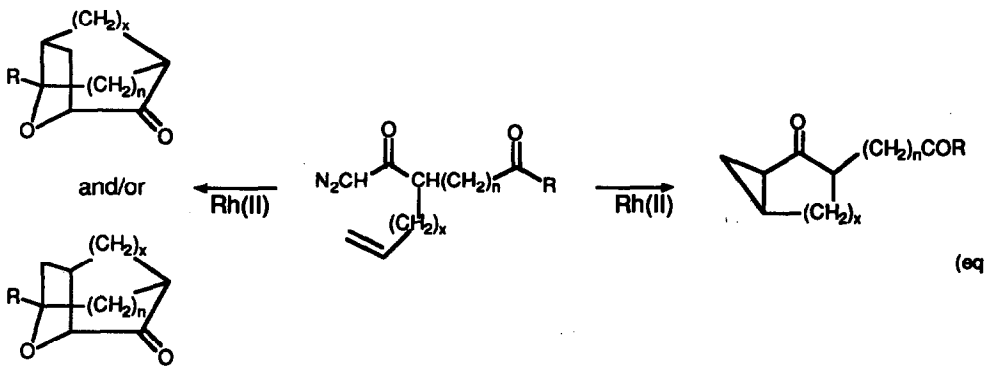
Abstract: *Ligand substitution in the rhodium (II) catalyzed decomposition of α-diazo ketones containing tethered alkenes results in differing product ratios for intramolecular dipolar cycloaddition and cyclopropanation.*

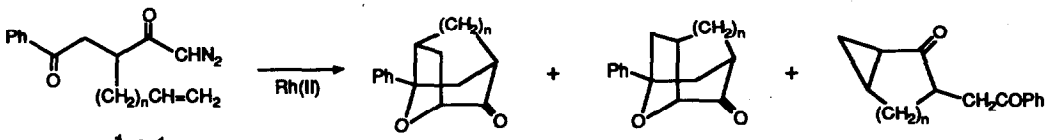
Electrophilic carbene complexes are of interest as highly reactive intermediates for metal catalyzed cycloaddition reactions, for which there is considerable synthetic utility.[1-5] Previous papers from these laboratories have described a route to oxapolycyclic ring systems which involves the tandem cyclization-cycloaddition reaction of a rhodium carbenoid intermediate derived from a α-diazo carbonyl compound.[6] More recently, in a collaborative effort with the Doyle group, the ability of dirhodium (II) ligands to determine reaction preference toward two different functional groups within the same molecule was examined.[7] By changing the dirhodium (II) ligand from acetate to trifluoroacetate (or caprolactam), the reaction pathway could be markedly altered (eq. 1). As a continuation of our studies in this area, we have found that, in certain cases, regiochemical control of the intra-



(eq 1)

molecular cycloaddition process is also sensitive to the bridging ligands of the rhodium (II) catalyst. In addition to ligand effects, the tether length of the pendant olefin also influences regiochemistry. Moreover, the regiochemical outcome of the reaction can be nicely predicted on the basis of computationally determined strain energies of the resulting cycloadducts.

In order to investigate the competition between cycloaddition *vs.* cyclopropanation, two model systems differing in tether length were examined. Both 3-allyl-2,5-diazopentanedione (**1**) and 3-butenyl-2,5-diazopentanedione (**5**) were allowed to react with a trace amount of rhodium (II) catalyst in methylene chloride at room temperature. Three major products were isolated corresponding to the internal trapping of a carbonyl ylide intermediate as well as intramolecular cyclopropanation.[8] Changing the catalyst from $Rh_2(OAc)_4$ (acetate) to $Rh_2(tfa)_4$ (trifluoroacetate) caused a significant alternation in product distribution with diazodione **1**; a rather startling and unexpected regiochemical cross-



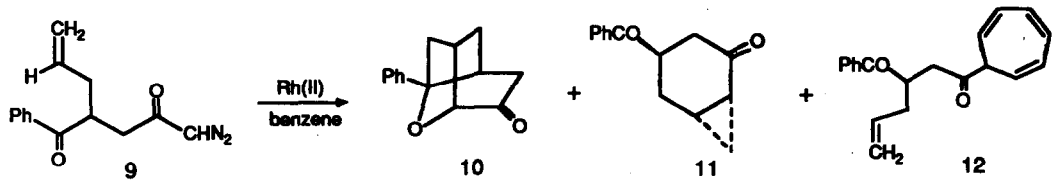
1; n=1	2; n=1	3; n=1	4; n=1
$Rh_2(OAc)_4$	10%	47%	37%
$Rh_2(tfa)_4$	34%	12%	30%
$Rh_2(cap)_4$	12%	52%	32%

5; n=2	6; n=2	7; n=2	8; n=2
$Rh_2(OAc)_4$	60%	11%	13%
$Rh_2(tfa)_4$	67%	0%	0%
$Rh_2(cap)_4$	70%	11%	17%

over being encountered. Cycloadduct **2** was the major product isolated when $Rh_2(tfa)_4$ was used, whereas cycloadduct **3** was the major regioisomer formed with the other two catalysts.[9] No regiochemical difference across the three Rh (II) catalysts was observed with the butenyl substituted system **5**. Intramolecular cyclopropanation occurs to a considerable extent with all catalysts in systems where a bicyclo[3.1.0] ring system is produced (**4**; n=1). The importance of this pathway diminishes with the bicyclo[4.1.0] ring system (**8**; n=2) and is presumably related to conformational/entropic factors.

The fact that the regiochemical distribution with diazodione **1** is influenced by the nature of the rhodium ligand is most remarkable. Regiochemical control in 3+2-dipolar cycloaddition reactions has generally been rationalized on the basis of FMO considerations.[10] For carbonyl ylides, the HOMO of the dipole is dominant for reactions with electron-deficient dipolarophiles, while the LUMO becomes important for cycloaddition to more electron-rich species.[11] Cyclization of the lone pair of electrons of the neighboring carbonyl group onto the reactive α-ketometallocarbene intermediate is believed to be followed by dissociation of the catalyst and generation of a non-metal complexed dipole.[12] However, the results encountered with diazodione **1** requires some mechanistic modification of this scheme. One possibility is that immediately after dipole generation, the $Rh_2(tfa)_4$ catalyst coordinates with the nearby olefinic π-bond.[13] This complexation may very well lower the LUMO energy of the tethered alkene and consequently shift the cycloaddition from a LUMO to a HOMO controlled process. Alternatively, the $Rh_2(tfa)_4$ catalyst may still be coordinated (η^2 or η^3) with the dipole and this metal complexed species could then undergo a subsequent intramolecular cycloaddition with a different regiochemical profile. Further work is necessary before one can distinguish between these two possibilities.

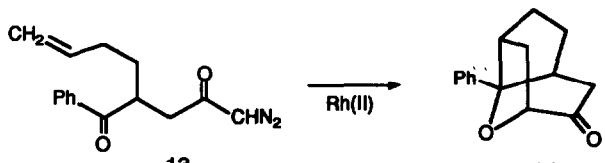
Decomposition of the isomeric 4-allyl-2,5-diazopentanedione **9** in benzene occurred readily in the presence of a catalytic amount of rhodium (II) acetate to give a single 3+2-cycloadduct (*i.e.*, **10**) as well as the product derived from cyclopropanation (**11**). Yields for cyclopropanation are consistently lower than those for cycloaddition, irrespective of the nature of the ligand. Bimolecular reaction with benzene occurs (*i.e.*, **12**) to the exclusion of carbonyl ylide generation or cyclopropanation with the carbene generated with $Rh_2(tfa)_4$.[14] What is so remarkable about this result is the degree to which chemoselectivity can be achieved over such a broad spectrum of carbene transformations by

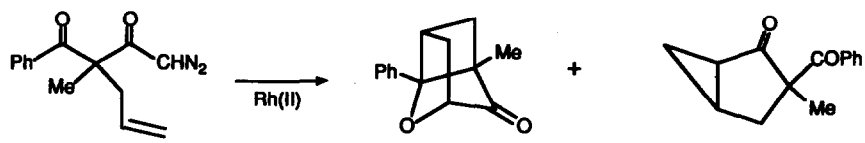


	10	11	12
$Rh_2(OAc)_4$	38%	38%	0%
$Rh_2(tfa)_4$	0%	0%	80%
$Rh_2(cap)_4$	43%	32%	0%

simply changing the dirhodium (II) ligand from an acetate to a trifluoroacetate group.

The exclusive formation of the 3+2-cycloadduct **14** from the reaction of 4-butenyl-2,5-diazopentanedione **13** with $Rh_2(OAc)_4$ (82%), $Rh_2(tfa)_4$ (78%) and $Rh_2(cap)_4$ (66%) is worth noting since it represents a regiochemical crossover in the approach of the alkene to the dipole. In the previous example (**9**→**10**), the alkenyl group approached the dipole from the side opposite to its own attachment while with the homologous system (**13**→**14**), the approach is from the same side of attachment. This crossover, as well as the regioselectivity found with 3-allyl-2,4-diazobutanedione **15** suggests that both steric and conformational factors play an important role in the control of regiochemistry. The structures of cycloadducts **14** and **16** were unequivocally established by X-ray crystallography.





	16	17
$Rh_2(OAc)_4$	60%	24%
$Rh_2(tfa)_4$	67%	0%
$Rh_2(cap)_4$	70%	28%

A computational approach to rationalize the observed product distribution was initiated. The thermodynamic stabilities of cycloaddition transition states can be approximated from the computationally derived strain energies of ground state molecules using traditional force-field techniques. Globally minimized ground state energies were obtained for all possible cycloaddition products using Bakmdl,[15] a Monte-Carlo statistical search method, and final strain energies were subsequently calculated using the MMX force field.[16] In the 3-substituted 2,5-diazo pentanedione system where both regioisomeric cycloadducts are observed, the MMX strain energy difference was calculated to be 0.55 kcal/mol for cycloadducts **2** and **3** and 0.67 kcal/mol for **6** and **7**. In systems where only one

regioisomer was formed, substantial energy differences were noted. The difference in strain energy for cycloadduct **10** relative to the alternative regioisomer was calculated to be 11.86 kcal/mol. Cycloadducts **14** and **16** were determined to be 4.34 and 3.55 kcal/mol more stable that the alternative regioisomers. Thus, in all the cases studied, the lower energy isomer corresponded to the cycloadduct actually isolated. This is a subtle effect which is not immediately obvious on inspection of molecular models but for which MM_2 calculations serve well to predict regiochemistry in such intramolecular dipolar-cycloadditions.

We are continuing to investigate the synthetic potential of dirhodium(II) ligand effects on chemoselectivity and will report additional findings at a later date.

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9. ^{1}H-NMR **2**: ($CDCl_3$, 300 MHz) δ 1.76-1.80 (m, 1H), 1.89 (d, 1H, J=12.5 Hz), 2.09-2.15 (m, 1H), 2.28 (dd, 1H, J=13.2 and 3.0 Hz), 2.37 (d, 1H, J=11.5 Hz), 2.45 (ddd, 1H, J=13.2, 4.8 and 2.3 Hz), 2.58 (brs, 1H), 3.10 (dd, 1H, J=11.5 and 5.5 Hz), 4.22 (dd, 1H, J=5.5 and 1.5 Hz), and 7.23-7.39 (m, 5H); ^{1}H-NMR **3**: $CDCl_3$, 300 MHz) δ 1.90 (dd, 1H, J=11.9 and 2.8 Hz), 1.95 (d, 1H, J=11.9 Hz), 2.19-2.26 (m, 1H), 2.27-2.34 (m, 1H), 2.37 (dd, 1H, J=11.8 and 3.4 Hz), 2.56 (dd, 1H, J=11.8 and 2.8 Hz), 2.88 (t, 1H, J=6.1 Hz), 2.92-2.89 (m, 1H), 4.39 (d, 1H, J=4.6 Hz), and 7.25-7.46 (m, 5H).
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