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Ligand effects in the Rh(II) catalyzed reaction of α-diazo ketoamides

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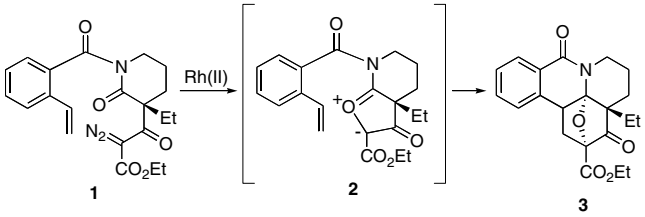
Abstract—The rhodium(II) catalyzed decomposition of several α-diazo ketoamides resulted in either formation of a push–pull carbonyl ylide intermediate followed by intramolecular [3+2]-cycloaddition across the tethered π-bond or C–H insertion of the initially formed rhodium carbenoid into the C_5-position of the lactam ring followed by a carboethoxy-decarboxylation reaction. The chemoselectivity exhibited by the rhodium carbenoid intermediate was found to be markedly dependent on the metal ligands employed.

Rhodium(II) carboxylates are particularly effective catalysts for the decomposition of α-diazo carbonyl compounds and many chemical syntheses are based on this methodology.[1–3] Among the more synthetically useful processes of the resulting carbenoid intermediates are intramolecular C–H insertion reactions.[4,5] It is generally found that five-membered ring formation is kinetically favored in the reaction of flexible, acyclic diazocarbonyl systems, whereas four- and six-membered ring formation are rarely observed. Much effort has been directed toward understanding the factors that control the regio and stereoselectivities in C–H insertion reactions.[4,5]

The generation of onium ylides by transition-metal promoted cyclization has also emerged as an important method for the assembly of ring systems that are difficult or impossible to prepare by other means.[2,3] Construction of polyheterocycles through metal intervention has been a particularly fruitful area of investigation, and the synthesis of various types of natural products by this approach has been carried out by several investigators.[6,7] Recent papers from these laboratories have described a route to azapolycyclic ring systems that involves a tandem *cyclization–cycloaddition* of a transient rhodium carbenoid.[8] This reaction is an integral part of our program aimed at developing new cascade reactions and achieving the total syntheses of various nitrogen-containing heterocycles.[9] Our more recent achievements in this area involve the use of diazo ketoamides such as **1** (Scheme 1).[10] Intramolecular attack of the amido carbonyl oxygen at the rhodium carbenoid center produces a push–pull stabilized carbonyl ylide intermediate (**2**). Subsequent [3+2]-cycloaddition across the tethered vinyl group furnished cycloadduct **3** in 95% isolated yield, thereby demonstrating the facility of the cascade reaction.

In earlier work from our laboratory we had described a synthetic route to 4-oxo-6,7-dihydrovindorosine that proceeded by a related [3+2]-cycloaddition across a tethered indole ring.[11] In the context of extending the above cycloaddition reactions to other ring systems, we wondered whether the push–pull dipole might also undergo intramolecular dipolar cycloaddition with different heteroaromatic π-bonds. With this in mind, we carried out the Rh(II)-pivalate catalyzed reaction of the *N*-thiophene substituted-3-diazo ketoamide **4** at 90 °C in benzene and found that the desired cycloadduct **5** was produced, but only in 35% yield (Scheme 2). No other



Scheme 1.

Keywords: Diazo; Ketoamide; Rhodium; Catalyst; Ligand; Effect; Intramolecular; Cycloaddition; C–H insertion.
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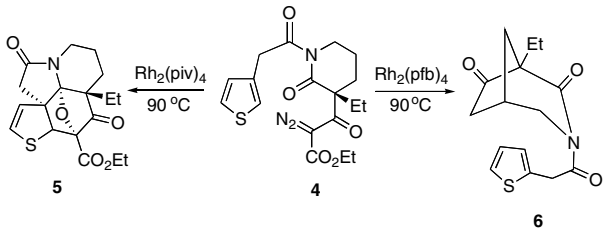
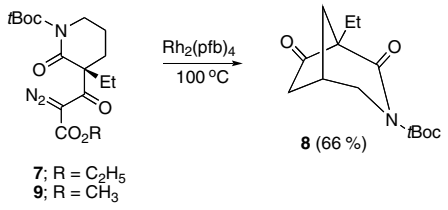


Scheme 2.

characterizable product could be detected in the crude reaction mixture. The lower yield encountered with this system is probably related to the high aromaticity of the thiophene ring, which needs to be overcome in the [3+2]-cycloaddition reaction. Thiophene possesses a low lying HOMO energy level, which increases the energy gap between the interacting FMOs and therefore diminishes the rate of the overall [3+2]-cycloaddition relative to other systems containing simple π-bonds.[12]

While searching for optimal reaction conditions to maximize the yield of cycloadduct **5**, we found that changing the ligand group on the rhodium catalyst resulted in a major difference in the overall reaction pathway. Thus, the only compound that was isolated from the rhodium(II)-perfluorobutyrate ($Rh_2(pfb)_4$) catalyzed decomposition of **4** (90 °C microwave) was lactam **6** (51%), which arose from a formal insertion of the metal carbene into the C–H bond at the 5-position of the lactam ring followed by an unusual ethoxy-decarboxylation reaction (vide infra). No signs of the previously isolated cycloadduct **5** were detected in the crude reaction mixture. The structure of lactam **6** was assigned on the basis of its characteristic spectral data.

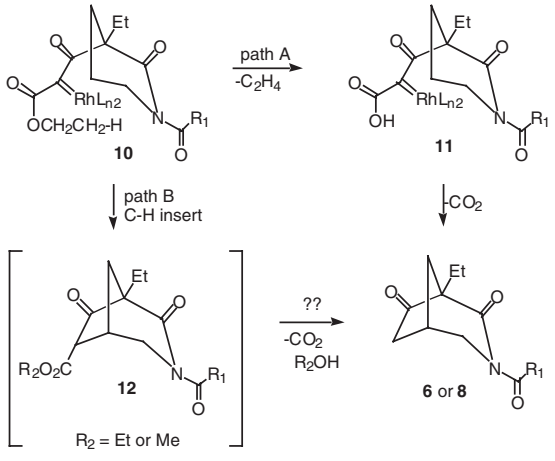


Scheme 3.

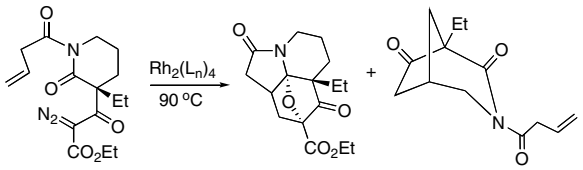
Formation of the 3-aza-bicyclo[3.2.1]octan-2,7-dione ring system was found to be a general reaction that also occurred with related α-diazo ketoamides just as long as $Rh_2(pfb)_4$ was used as the catalyst. Thus, the rhodium(II) perfluorobutyrate catalyzed decomposition of diazo ketoamide **7** at 100 °C in benzene afforded the analogous insertion product **8** in 66% isolated yield (Scheme 3). The structure of **8** was assigned on the basis of its spectral properties, in particular, the ^1H NMR spectrum which showed the methyl group as a triplet at 0.84 ($J = 7.2$ Hz), the *t*-Boc group as a singlet at 1.50 (9H), and doublet of quartets for the diastereotopic methylene hydrogens of the ethyl group at 1.72 and 2.10, one of the bridge methylene hydrogens at 2.06 (ddd, $J = 12.0$, 3.0 and 1.5 Hz), the other bridge hydrogen at 2.19 (dd, $J = 12.0$ and 3.0 Hz), an ABX pattern at 2.39 (dd, $J = 19.0$ and 2.4 Hz) and 2.55 (dd, $J = 19.0$ and 7.8 Hz), a multiplet for the bridgehead proton at 2.88 and another ABX pattern at 3.59 (dd, $J = 12.5$ and 1.5 Hz) and 3.85 (dd, $J = 12.5$ and 3.0 Hz). When the reaction of **7** was carried out using $Rh_2(OAc)_4$ as the catalyst, there were no detectable quantities of lactam **8** or any other characterizable product; thereby attesting to the sensitivity of the C–H insertion reaction to the nature of the ligand group attached to the rhodium metal.

One conceivable route to account for aza-bicyclo lactam formation involves the production of ethylene from the initially formed rhodium carbenoid **10** followed by C–H insertion and eventual extrusion of CO_2 (path A). To test this mechanistic possibility, we prepared the corresponding methyl ester (i.e., **9**) and noted no significant difference in the yield of product when **9** was treated with the $Rh_2(pfb)_4$ catalyst. It is for this reason that we propose the alternate mechanism (path B) shown in Scheme 4, which involves initial C–H insertion into the 5-position of the lactam ring followed by a subsequent hydrolysis/decarboxylation reaction. Unfortunately, all of our efforts to detect the expected intermediate **12** failed to indicate its presence in the reaction mixture. Since it was necessary to carry out the catalyzed reaction at elevated temperatures (>90 °C) for the C–H insertion to proceed, we assume that **12** is simply too labile to be detected under the thermal conditions employed. Further work is clearly necessary before this pathway can be unequivocally established.

Earlier studies have shown that, despite their high reactivity, rhodium carbenoid intermediates are often highly chemoselective when two or more reaction pathways are open to them.[13] Site selectivity has been found to depend not only on the type of α-diazocarbonyl utilized, but is also governed by steric,[14–17] conformational[18] as well as electronic factors.[19–22] The earlier studies have revealed some interesting ligand effects, and it is now established that carboxylate ligands can effectively control chemoselectivity in competitive carbenoid transformations of α-diazocarbonyl compounds.[2c] In order to further investigate the chemoselectivity of the reaction as a function of the nature of the catalyst, we prepared



Scheme 4.



	14	15
L_n = piv	98%	0%
L_n = cap	98%	0%
L_n = OAc	91%	4%
L_n = man	88%	6%
L_n = tfa	73%	22%
L_n = pfb	62%	32%

Scheme 5.

the *N*-but-3-enoyl substituted imide **13**, which possesses an unactivated terminal π-bond. The rhodium(II) pivalate catalyzed decomposition of **13** resulted in exclusive carbonyl ylide formation and subsequent intramolecular cycloaddition to give cycloadduct **14** in 98% yield. No signs of any product derived from a C–H insertion could be detected in the crude reaction mixture. Virtually complete cycloaddition chemistry also occurred when rhodium(II) caprolactomate ($Rh_2(cap)_4$) was used as the catalyst. Although Rh(II) acetate ($Rh_2(OAc)_4$) and Rh(II) mandelate ($Rh_2(man)_4$) also afforded cycloadduct **14** as the major product, small amounts of the C–H insertion product **15** could be detected in the crude reaction mixture. Catalysis by Rh(II) trifluoroacetate ($Rh_2(tfa)_4$) or $Rh_2(pfb)_4$, on the other hand, gave significant quantities of the insertion product **15** (22% and 32%). The variation in reactivity (yield) presumably reflects the differences in electrophilicity between the various rhodium carbenoid intermediates. Intramolecular C–H insertion is enhanced with the more electrophilic carbene generated using $Rh_2(pfb)_4$, as had been encountered earlier with allyl and aryl substituted 1-diazopentanediones.[13b] Either charge or HOMO/LUMO control or both may be operating in these Rh(II)-catalyzed transformations (Scheme 5).

In conclusion, several trends have surfaced from our investigations in this area. First and foremost, these studies have demonstrated that the intramolecular tandem cyclization–cycloaddition cascade of α-diazo ketoamides is a viable method for quickly assembling complex oxapolycyclic ring systems from easily prepared precursors. Both alkenyl and tethered thiophene groups undergo the cycloaddition. In addition, ligand substitution in the rhodium(II) catalyst can markedly alter the product ratio between [3+2]-cycloaddition and intramolecular C–H insertion. Ongoing investigations will further clarify the controlling factors in rhodium(II)-catalyzed reactions with additional examples that amplify the degree to which selectivity can be achieved.

Acknowledgements

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