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HIGHLY SELECTIVE γ-LACTONE SYNTHESES BY INTRAMOLECULAR CARBENOID CARBON-HYDROGEN INSERTION IN RHODIUM(II) CARBOXYLATE AND RHODIUM(II) CARBOXAMIDE CATALYZED REACTIONS OF DIAZO ESTERS

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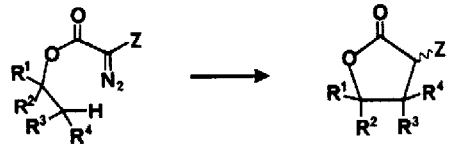
Summary: Rhodium(II) acetate and rhodium(II) acetamide catalyzed decomposition of diazo esters forms γ-lactones in high yield and with exceptionally high regio- and diastereoselectivity.

Despite the convenience of their synthesis and the now well known ability of diazo ketones to undergo intramolecular C-H insertion reactions,[1,2] diazo esters have rarely been successfully employed for these carbon-carbon bond forming reactions. Carbenoid decomposition of diazo esters, if anologous to that of diazo ketones, should provide a convenient methodology for the synthesis of highly substituted γ-lactones (eq. 1). However, diazoacetate esters do not undergo C-H insertion in copper catalyzed reactions to any meaningful extent,[3] and even the

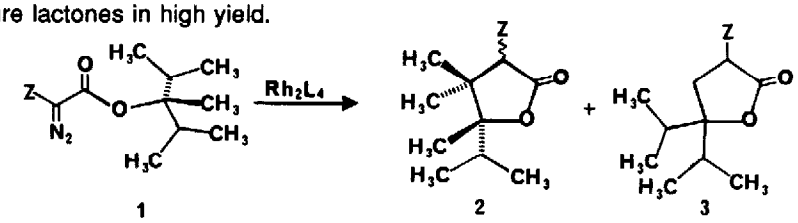


(1)

more viable diazomalonate esters produce γ-lactones in only low to moderate yields in the few examples that have been published.[4] Recently, Adams and coworkers reported that an oxygen heteroatom activates the adjacent C-H bond for carbenoid insertion in rhodium(II) acetate catalyzed reactions,[5] and they have successfully exploited this process for the synthesis of 3(*2H*)-furanones.[6] In the single example of an intramolecular C-H insertion reaction of a diazo ester catalyzed by $Rh_2(OAc)_4$ and directed to the synthesis of pentalenolactone E,[7] Cane and Thomas found the desired δ-lactone as the predominant product rather than the normally favored γ-lactone, whose formation was apparently sterically restricted. Capitalizing on the directive influences that can be achieved by variation of the bridging ligands of rhodium(II) carboxylates and rhodium(II) carboxamides,[8] we now report that catalytic carbenoid decomposition of diazo esters provides a convenient, general, and highly selective methodology for the

synthesis of γ-butyrolactones.

Diazo esters were prepared in high yield from the corresponding alcohols by condensation with diketene,[9] diazo transfer using methanesulfonyl azide,[10] and, for diazoacetate syntheses, deacylation by treatment with aqueous potassium hydroxide.[11] Treatment of 2,3,4-trimethyl-3-pentyl diazoacetate (**1**, Z = H) in dichloromethane at room temperature with $Rh_2(OAc)_4$ resulted in the production of nearly equal amounts of two γ-lactone products, **2** and **3** (eq. 2, Z = H). Reactions were performed by the controlled addition of the diazo compound to a dichloromethane solution containing 1.0 mol % of the rhodium(II) catalyst. Formation of fumarate and maleate esters was competitive with intramolecular C-H insertion and accounted for 16% of the 97% weight yield of the isolated product. Chromatographic separation of the catalyst on alumina followed by distillation of the reaction products allowed isolation of the chromatographically pure lactones in high yield.

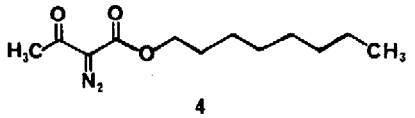


1 **2** **3** (2)

Rh_2L_4	Z = H yield,%	relative yield,% **2**	**3**	Z = CH_3CO yield,%	relative yield,% **2**	**3**
$Rh_2(pfb)_4$	56	32	68	45	45	55
$Rh_2(OAc)_4$	81	53	47	97	90	10
$Rh_2(acam)_4$	96	>99	<1	89	>99	<1

The formation of **3** is surprising in view of the high selectivity for insertion into 3° C-H bonds that has been reported for cyclopentanone formation by intramolecular carbenoid insertion in copper and $Rh_2(OAc)_4$ catalyzed decompositions of diazo carbonyl compounds.[12,13] Taber and Ruckle, in particular, have noted the preference for insertion as 3°>2°>>1° with no observed example of carbenoid reaction with a methyl group, and they explain these relative reactivities by electronic effects.[13] In $Rh_2(OAc)_4$ catalyzed reactions of **1** (Z = H), insertion occurs with approximately statistical preference. However, by changing the catalyst from $Rh_2(OAc)_4$ to the less discriminate $Rh_2(pfb)_4$ (pfb = perfluorobutyrate)[14] and to the electronically selective $Rh_2(acam)_4$ (acam = acetamide),[8] significant manipulation of the product distribution could be achieved, and with $Rh_2(acam)_4$ as the catalyst **2** is formed as the sole product. Qualitatively similar results are obtained from catalytic decomposition of the acyl derivative (**1**, Z = CH_3CO) whose selectivity in carbenoid reactions is normally regarded to be higher than that of its deacylated analog and which is less prone to carbene dimer formation. Once again, $Rh_2(pfb)_4$ gives a nearly statistical distribution of products while $Rh_2(acam)_4$ catalyzes the exclusive formation of **2** (Z = CH_3CO).[15]

Extension of this methodology to **4** produced **5** in 85-88% yield, as the sole lactone product from $Rh_2(OAc)_4$ or $Rh_2(acam)_4$ catalyzed decompositions,[16] but fumarate and maleate esters were the major products from the catalytic decomposition of **6** that was performed under



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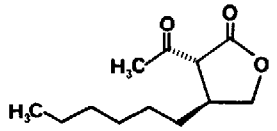

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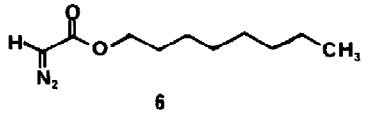
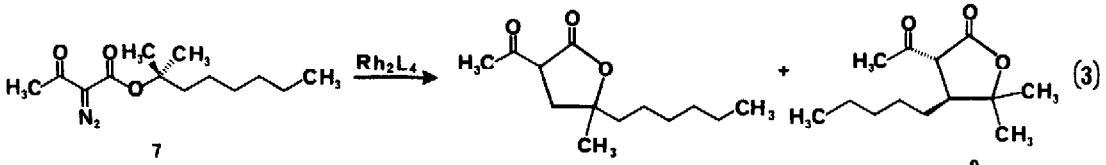


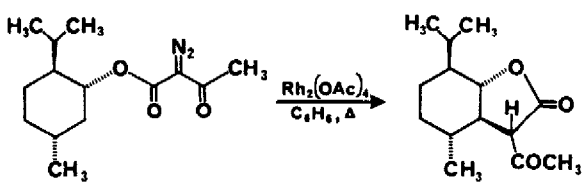
6

the same reaction conditions. With **7** competition between C-H insertion into 2° and 1° positions was observed (eq. 3), and **8** was favored in $Rh_2(pfb)_4$ catalyzed reactions (81% yield; **8**/**9** = 1.7)



7 **8** **9** (3)

while **9** was dominant in those promoted by either $Rh_2(OAc)_4$ (80% yield; **9**/**8** = 2.6) or $Rh_2(acam)_4$ (80% yield; **9**/**8** = 7.3). Based on results with **1** (Z = CH_3CO) and **7**, relative reactivities for C-H insertion follow the order 3°>2°>1° that was reported by Taber and Ruckle,[13] but with significantly enhanced numerical values (54:7.7:1.0 for $Rh_2(OAc)_4$). However, these relative reactivities are of no practical value in predicting the outcome of C-H insertion reactions in more complex systems where stereoelectronic or steric factors govern product formation. For example, $Rh_2(OAc)_4$ catalyzed decomposition of (1R,2S,5R)-(-)-menthyl diazoacetoacetate (**10**) resulted in the exclusive formation of bicyclic γ-lactone **11** which was isolated in 80% yield. The trans ring fusion and acetyl group stereochemistry were established by NMR analysis (coupling constants of 10.7 and 12.4 Hz, respectively).[17]



10 **11** (4)

High product yields and the exceptional regio- and stereoselectivity for γ-lactone formation afforded by rhodium(II) catalysts in reactions with diazo esters provides a convenient methodology for remote functionalization. The scope and mechanism of this transformation are currently under investigation.

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15. Only one stereoisomer of **2** is observed by capillary GC and NMR analyses.
16. No evidence for β-lactone formation, despite the reported C-H activation by the ether oxygen,[5,6] was obtained.
17. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.71 (t, J = 10.7 Hz, C*H*O), 3.44 (d, J = 12.4 Hz, C*H*CO), 2.41 (s, CH_3CO), 2.31 (d of t, J = 12.4, 10.7, 10.7 Hz, 1H), 2.00-1.88 (m, 1H), 1.84-1.62 (m, 3H), 1.58-1.38 (m, 1H), 1.23-1.00 (m, 2H), 0.95 (d, J = 7.0 Hz, 3H), 0.89 (d, J = 7.0 Hz, 3H), and 0.82 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 202.0, 172.5, 84.5, 58.7, 52.2, 46.6, 35.4, 34.4, 30.6, 28.6, 25.0, 19.8, 19.7, and 17.8; m.p. 98-99°C; $[\alpha]_D^{24°}$ = - 33.4° (c = 0.59, $CHCl_3$). Satisfactory elemental analyses for this and other lactone products described in this communication were obtained.

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