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CONFORMATIONAL AND ELECTRONIC PREFERENCES IN RHODIUM(II) CARBOXYLATE AND RHODIUM(II) CARBOXAMIDE CATALYZED CARBON-HYDROGEN INSERTION REACTIONS OF *N,N*-DISUBSTITUTED DIAZOACETOACETAMIDES

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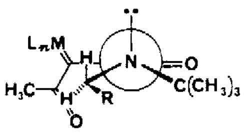
Summary: Conformational preferences dominate electronic influences in governing regioselectivity for catalytic C-H insertion reactions of diazoacetoacetamides and allow the construction of β-lactams by insertion α and β to an ester functional group.

We have recently reported a new methodology for the synthesis of β-lactam compounds through intramolecular carbon-hydrogen insertion caused by rhodium(II) acetate catalyzed decomposition of *N*-benzyl and *N*-alkyl diazoacetoacetamides.[1] The success of this transformation was attributed to conformational preferences which placed the reacting C-H bond in close proximity to the carbenoid center (**1**).



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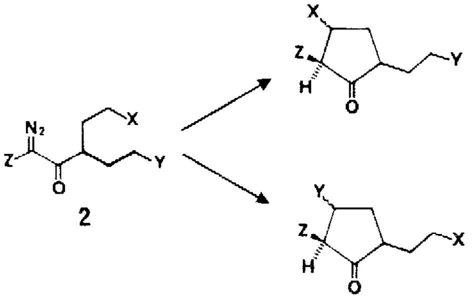

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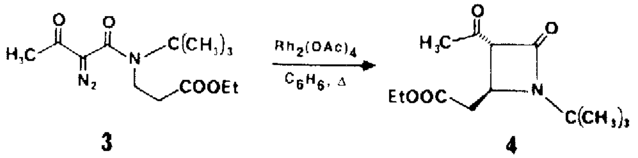
(1)

However, Tabor and Ruckle[2] and, more recently, Stork and Nakatani[3] have reported that electronic factors, rather than conformational preferences, control reactivity and, consequently, selectivity in C-H insertion reactions of α-diazoketones (**2**). In their studies of cyclopentanone formation, electron withdrawing substituents were shown to decrease the reactivity of adjacent C-H bonds towards insertion, relative to similarly substituted C-H bonds without electron withdrawing substituents at the same formal distance from the carbenoid center (eq. 1). Since this interpretation leads to conclusions regarding regiocontrol in insertion reactions that are different from those predicted by conformational preferences, we have undertaken investigations designed to probe the factors that govern regiocontrol in intramolecular C-H insertion reactions resulting from the catalytic decomposition of *N,N*-disubstituted diazoacetoacetamides.

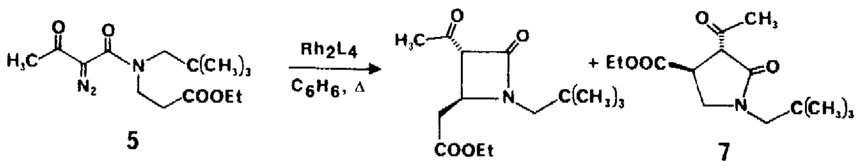
In one of the most dramatic demonstrations of regiocontrol by electron withdrawing groups, Stork and Nakatani found that an ester substituent deactivates both α- and β-methylene groups towards C-H insertion so that, even when this intramolecular pathway is the only one possible, only carbene dimer formation is realized.[3] Consequently, we were surprised to find that **3** undergoes $Rh_2(OAc)_4$-catalyzed



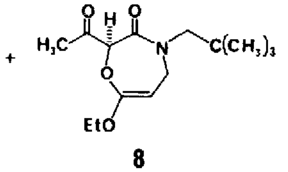
(2)

decomposition in refluxing benzene to yield β-lactam **4** in 96% yield (eq. 2). The exclusive formation of the trans isomer of **4** was established from its NMR spectrum which exhibited coupling constants of 2.1 Hz for hydrogens on the β-lactam ring:[4] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.23 (d of d of d, J = 2.1, 3.8, 9.3 Hz, 1H), 4.07 and 4.06 (two q, J = 7.2, 7.2 Hz, 2H), 3.90 (d, J = 2.1 Hz, 1H), 2.85 (d of d, J = 15.6, 3.8 Hz, 1H), 2.50 (d of d, J = 15.6, 9.3 Hz, 1H), 2.22 (s, 3H), 1.27 (s, 9H), and 1.15 (t, J = 7.2 Hz, 3H).

When the *tert*-butyl group of **3** was replaced by neopentyl to allow the possibility of C-H insertion into its electronically activated CH_2 group, catalytic decomposition of **5** formed three products identified as the β- and γ-lactams (**6** and **7**),[5] produced by C-H insertion into the CH_2 groups β and α to the deactivating ester substituent, and **8**[6] (eq. 3) which was presumably derived from the metal associated carbonyl ylide **9** by a formal 1,7-hydrogen migration (eq. 4) that occurs because of the orientation of the acetyl carbonyl group near to a hydrogen on the carbon α to the ester (**9a**).[7] By changing the catalyst



Rh_2L_4	Total Yield,%	relative yield, %		
		6	7	8
$Rh_2(pfb)_4$	95	20	4	76
$Rh_2(OAc)_4$	90	50	12	38
$Rh_2(acam)_4$	93	56	16	28



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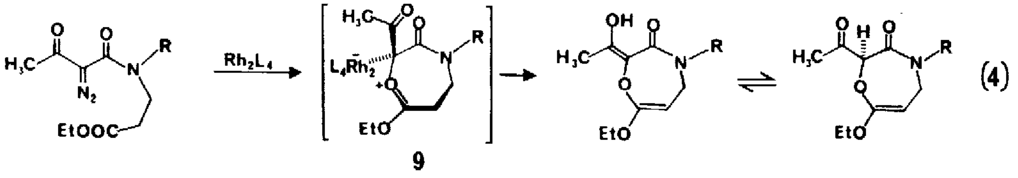

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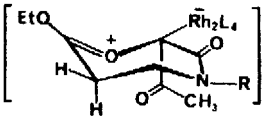
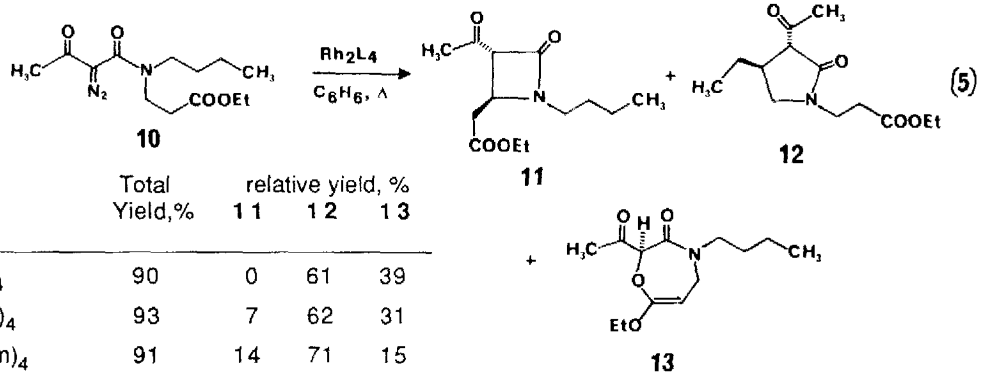
9a



from the indiscriminate $Rh_2(pfb)_4$ (pfb = perfluorobutyrate)[8] through $Rh_2(OAc)_4$ to the electronically selective $Rh_2(acam)_4$, (acam = acetamide),[9] significant manipulation of the product distribution could be achieved. However, in no case could the product from C-H insertion into the neopentyl methylene group be identified as a significant component in the product mixture (<5% yield). In this example, as with the carbenoid intermediate derived from **3**, only the β-propionate substituent of the amide lies in close proximity to the metal carbene center and, as suggested from the conformational preference exemplified in **1**, C-H insertion occurs into C-H bonds that are β- or α- to the deactivating ester substituent. Carbonyl ylide formation with the ester carbonyl group (**8**), a process that is not common with diazoketoesters in $Rh_2(OAc)_4$-catalyzed reactions,[10] is a competitive reaction in the decomposition of **5**, and its importance increases with the electron withdrawing capabilities of the bridging ligands of the dirhodium(II) catalyst.

Whereas with **3** and **5** the more favorable conformation of the reacting metal carbene intermediate places the β-propionate substituent close to the carbenoid center, the comparable sizes of *n*-butyl and β-propionate substituents in the metal carbene derived from **10** would suggest that there should be a distribution of products resulting from reactions with both amide substituents. This is indeed what is observed (eq. 5). Carbon-hydrogen insertion and/or carbonyl ylide formation/rearrangement (**11** and **13**)[11] with the β-propionate substituent account for up to 39% of the reaction products. γ-Lactam **12** is the sole product from C-H insertion into the *n*-butyl substituent. Although an ester substituent clearly decreases the reactivity of its α-C-H bond towards carbenoid insertion, this inhibition exists relative to both β-C-H insertion and carbonyl ylide formation, both of which compete favorably for capture of the β-propionate substituent. Catalyst dependent carbenoid reactivity, although markedly affecting the competition for formation of **11** and **13**, does not substantially alter the product distribution from reactions with the *n*-butyl and β-propionate substituents of the amide.

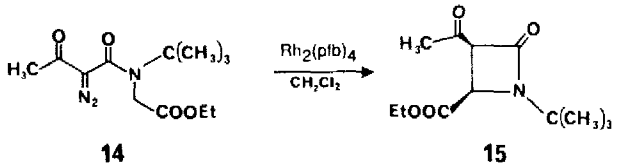


10 **11** **12** **13**

(5)

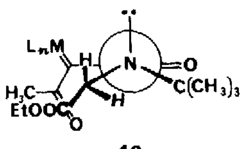
Rh_2L_4	Total Yield,%	relative yield, % 11	12	13
$Rh_2(pfb)_4$	90	0	61	39
$Rh_2(OAc)_4$	93	7	62	31
$Rh_2(acam)_4$	91	14	71	15

Finally, in what is the most convincing demonstration of conformational preferences in carbenoid insertion reactions, diazoacetoacetamide **14** underwent high yield conversion (89%) to β-lactam **15** in $Rh_2(pfb)_4$ catalyzed reactions performed in refluxing dichloromethane (eq. 6). The cis stereochemistry of **15** is suggested from its ^1H NMR spectrum[12] and by isomerization of **15** to its trans stereoisomer. The exclusive formation of **15** is consistent with the orientation of the intermediate metal carbene that is



14 **15**

(6)



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depicted in **16**. The synthetic versatility of this methodology is now amply demonstrated in the synthesis of both **4** and **15**, each of which are formed in exceptionally high yield and with extraordinary stereochemical control.

In acyclic systems such as **2**, the possibility exists that regiocontrol is a function of conformational preferences resulting from the relative attraction of substituent X or Y to the face of the catalyst rather than of inductive effects of X or Y.

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5. **6**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.38 (d of d of d, J = 7.8, 5.0, 2.2 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 4.05 (d, J = 2.2 Hz, 1H), 3.31 (d, J = 16.4 Hz, 1H), 3.20 (d, J = 16.4 Hz, 1H), 2.80 (d of d, J = 15.7, 5.0 Hz, 1H), 2.55 (d of d, J = 15.7, 7.8 Hz, 1H), 2.34 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H), and 0.94 (s, 9H). **7**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.18 (q, J = 7.1 Hz, 2H), 3.93 (d, J = 6.1 Hz, 1H), 3.78 (d of d of d, J = 7.9, 6.6, 6.1 Hz, 1H), 3.70 (d of d, J = 9.8, 7.9 Hz, 1H), 3.60 (d of d, J = 9.8, 6.6 Hz, 1H), 3.04 (s, 2H), 2.49 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H), and 0.93 (s, 9H).
6. **8**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.97 (d of d, J = 4.0, 3.0 Hz, 1H), 4.81 (s, 1H), 4.17 (d of d, J = 17.0, 3.0 Hz, 1H), 3.97 (d of d, J = 4.0 Hz, 1H), 3.82 (q, J = 7.0 Hz) and 3.79 (q, J = 7.0 Hz) for CH_2O, 3.61 (d, J = 17.2 Hz, 1H) and 3.51 (d, J = 17.2 Hz, 1H) for CH_2N, 2.26 (s, 3H), 1.32 (t, J = 7.0 Hz, 3H), and 0.97 (s, 9H).
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11. Spectral analyses are consistent with the assigned structures.
12. **15**: ^{1}H NMR (CDCl3, 300 MHz) δ 4.18 (d, J = 10.4 Hz, 1H), 3.60 (d of q, J = 8.6,7.0 Hz, 1H), 3.48 (d, J = 10.4 Hz, 1H), 3.41 (d of q, J = 8.6,7.0 Hz, 1H), 2.31 (s, 3H), 1.52 (s, 9H), and 1.28 (t, J = 7.0 Hz, 3H).

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