Rh(II)-Catalyzed Reaction Of Some α′,α′- and β′-Branched-*O*-Alkyl α-(Alkoxycarbonyl)-α-diazoacetates

Andrew G. H. Wee* and Qing Yu

Department of Chemistry, University of Regina, Regina, Saskatchewan, S4S 0A2, Canada

Received August 1, 1996 (Revised Manuscript Received February 25, 1997[⊗]*)*

α′,α′- and β′- Branched-*O*-alkyl α-(alkoxycarbonyl)-α-diazoacetates **1a**,**b** and **2a**,**b** were prepared. The regio- and chemoselectivities in the Rh(II)-catalyzed reaction of these compounds were studied. The model systems **1a**,**b** showed that the reactivity of the ester-substituted Rh(II) carbenoid is responsive to the nature of the Rh(II) catalyst; rhodium(II) acetamide favored insertion into the tertiary C−H bond and rhodium(II) perfluorobutyrate favored insertion into the secondary C−H bond. We also found that the nature of the *O*-alkyl group in the ester moiety had no influence on the reactivity of the Rh(II) carbenoid. In more complex systems such as compounds **2**, it was found that rhodium(II) acetate promoted insertion into tertiary C−H bonds. Intramolecular cyclopropanation, to give 3-oxabicyclo[5.1.0]octane and 3-oxabicyclo[6.1.0]nonane products, was found to be competitive with tertiary C−H insertion; it is favored when rhodium(II) perfluorobutyrate was used as the catalyst. The Rh(II)-catalyzed reaction of **3** ("carbon" analog of **2a**) resulted mainly in the cyclopentanone derivative, and no cyclopropanation product was detected. This result indicates that the ester oxygen in compounds of type **2** plays an important role in influencing the regio- and chemoselectivities of their reaction. Overall the results indicate that for compounds of a particular type of structure the regio- and chemoselectivities can be controlled via the judicious choice of the Rh(II) catalyst.

The intramolecular Rh(II) carbenoid C−H insertion reaction has emerged as a useful method in organic synthesis especially in ring-forming reactions.[1] 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 chemoselectivities in metallocarbenoid C−H insertion reactions. It is now clear that electronic effects transmitted from substituents adjacent to the site of C−H insertion play an important role in governing selectivities of the C−H insertion in competitive carbenoid reactions.[1,2] Studies have also indicated that the nature[3] as well as the steric size[4] of the bridging ligands on the dirhodium(II) metal have a marked influence on the regio- and chemoselectivities of the reaction. Nevertheless, steric and conformational effects that are inherent within a particular system can override these controlling factors, and in these situations the regio- and chemoselectivities of the reaction are less predictable.

Substituted γ-lactones are useful intermediates in natural product synthesis.[5] In connection with our interest in the use of 4,4-disubstituted-γ-lactones in alkaloid synthesis we have investigated the intramolecular Rh(II) carbenoid-mediated tertiary C−H insertion reaction of unsymmetrically substituted *O*-alkyl α-(methoxycarbonyl)-α-diazoacetates. Presently there is a paucity of data on the Rh(II) carbenoid-mediated tertiary C−H insertion in diazo esters. Most studies reported to date have described Rh(II) carbenoid C−H insertion in α-branched systems.[3b,c] On the other hand, C−H insertion reaction in β-branched systems are limited to simple model systems.[3a,d,i,5a] Herein, we report the results from our studies on the competitive Rh(II)-carbenoid mediated C−H insertion reaction in some α′,α′- and β′-branched-*O*-alkyl α-(alkoxycarbonyl)-α-diazoacetates typified by **1a**,**b** and **2a**,**b**. The goals of these studies are to define reaction conditions that are conducive for tertiary C−H insertion so that 4,4-disubstituted γ-lactones can be prepared. Using the model systems **1a**,**b**, we established that the ester-substituted metallocarbenoid is responsive to the nature of the ligand in the dirhodium(II) catalyst. We then directed our attention to the Rh(II) carbenoid-mediated reactions in **2a**,**b**. We found that the use of

[⊗] Abstract published in *Advance ACS Abstracts,* April 1, 1997.

(1) Reviews: (a) Doyle, M. P. *Comprehensive Organometallic Chemistry II*, Hegedus, L. S., ed., Pergamon Press: New York, 1995; Volume 12, Chap. 5.2. (b) Padwa, A.; Austin, D. J. *Angew. Chem., Int. Ed. Engl.*, **1994**, *33*, 1797. (c) Ye, T.; Mckervey, M. A. *Chem. Rev.* **1994**, *94*, 1091. (d) Padwa, A.; Krumpe, K. E. *Tetrahedron* **1992**, *48*, 5385. (e) Adams, J.; Spero, D. M. *Tetrahedron* **1991**, *47*, 1765. (f) Taber, D. F. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds., Pergamon Press: New York, 1991; Volume 3, Chapter 4.2. (g) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919.

(2) (a) Taber, D. F.; Ruckle, R. E. *J. Am. Chem. Soc.* **1986**, *108*, 7686. (b) Taber, D. F.; You, K. K.; Rheingold, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 547; see also footnote 20. (c) Wang, P.; Adams, J. *J. Am. Chem. Soc.* **1994**, *116*, 3296 and references cited therein. (d) Stork, G.; Nakatani, K. *Tetrahedron Lett.* **1988**, *29*, 2283.

(3) (a) Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958. (b) Padwa, A.; Austin, D. J.; Price, A. T.; Semones, M. A.; Doyle, M. P.; Protopova, M.; Winchester, W. R.; Tran, A. *J. Am. Chem. Soc.* **1993**, *115*, 8669. (c) Padwa, A.; Austin, D. J.; Hornbuckle, S. F.; Semones, M. A.; Doyle, M. P.; Protopova, M. N. *J. Am. Chem. Soc.* **1992**, *114*, 1874. (d) Pirrung, M. C.; Morehead, Jr., A. T. *J. Am. Chem. Soc.* **1994**, *116*, 8991. (e) Brown, D. S.; Elliot, M. C.; Moody, C. J.; Mowlem, T. J.; Marino, J. P., Jr.; Padwa, A. *J. Org. Chem.* **1994**, *59*, 2447. (f) Doyle, M. P.; Zhou, Q. -L.; Raab, C. E.; Roos, G. H. P.; *Tetrahedron Lett.* **1995**, *36*, 4745. (g) Miah, S.; Slawin, A. M. Z.; Moody, C. J.; Sheehan, S. M.; Marino, J. P., Jr.; Semones, M. A.; Padwa, A.; Richards, I. C. *Tetrahedron* **1996**, *52*, 2489. (h) Estevan, F.; Lahuerta, P.; Perez-Prieto, J.; Stiriba, S. -E.; Ubeda, M. A. *Synlett* **1995**, 1121. (i) Doyle, M. P.; Bagheri, V.; Pearson, M. M.; Edwards, J. D. *Tetrahedron Lett.* **1989**, *30*, 7001.

(4) (a) Hashimoto, S.-I.; Watanabe, N.; Ikegami, S. *Tetrahedron Lett.*, **1992**, *33*, 2709. (b) Hashimoto, S.-I.; Watanabe, N.; Ikegami, S. *J. Chem. Soc., Chem. Commun.* **1992**, 1508.

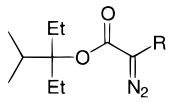
(5) For example: (a) Paquette, L. A.; Wang, T.-Z.; Sivik, M. *J. Am. Chem. Soc.* **1994**, *110*, 11323. (b) Takano, S.; Yonaga, M.; Morimoto, M.; Ogasawara, K. *J. Chem. Soc., Perkin Trans. 1*, **1985**, 305 and references cited therein. (c) Robin, J. P.; Gringore, O.; Brown, E. *Tetrahedron Lett.* **1980**, *21*, 2709. (d) Tomioka, T.; Kawasaki, H.; Iitaka, Y. *Tetrahedron Lett.* **1985**, *26*, 903. (e) Hanessian, S.; Murray, P. J.; Sahoo, S. P. *Tetrahedron Lett.* **1985**, *26*, 5623 and 5627. (f) Review of related works: Rao, Y. S. *Chem Rev.* **1976**, *76*, 625.

S0022-3263(96)01484-3 CCC: $14.00

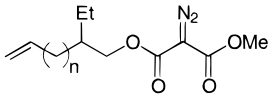
$Rh_2(OAc)_4$ as catalyst was optimal for promoting insertion into the tertiary C−H bond to give the corresponding 4,4-disubstituted γ-lactone products. Intramolecular cyclopropanation reaction of the double-bond in **2a**,**b** was found to be competitive with tertiary C−H insertion; $Rh_2(pfb)_4$ promoted intramolecular cyclopropanation over C−H insertion.

Results

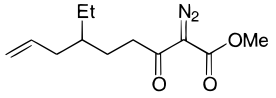
Compounds **1a**−**c** were prepared via acylation [α-(methoxycarbonyl)acetic acid, DCC[6a] or diketene, Et_3N[6b] in the case of **1c**] of 3-ethyl-2-methyl-3-pentanol[7] followed by diazotization[8] (MsN_3,[9] DBU) of the corresponding malonate or β-keto esters. The diazo compounds **2a,b** were readily prepared via alkylation of the dianion[10] of the appropriate carboxylic acid, followed by reduction with LAH to obtain the primary alcohol. Subsequent acylation[6a] of the primary alcohol with α-(methoxycarbonyl)-acetic acid provided the malonate esters. Diazotization[8] under standard conditions furnished the desired diazo compounds. α-Diazo-β-keto ester **3** was prepared from 4-ethyl-6-heptenoic acid.[11] Activation of the carboxylic acid group as the imidazolide (1,1′-carbonyldiimidazole, Et_3N) followed by reaction with the dianion[12] of α-(alkoxycarbonyl)acetic acid afforded the β-keto ester.[11] Subsequent diazotization[9] furnished **3**.



1 **a**; R = CO_2Me
b; R = $CO_2CH_2CF_3$
c; R = C(O)CH3



2 **a**; n = 1
b; n = 2



3

Our first aim was to determine whether the reactivity of the ester-substituted carbenoid can be modulated via the use of Rh(II) catalysts which possess bridging ligands that have different electronic demand. Thus we examined the regioselectivity (tertiary *vs* secondary) of γ-lactone formation in the reaction of **1a**,**b** (eq 1) with three different dirhodium(II) catalysts whose electronic demand ranges from strongly electron-withdrawing [$Rh_2(pfb)_4$] to electron-donating [$Rh_2(acam)_4$]; the electronic demand of $Rh_2(OAc)_4$ generally falls in between the two aforementioned catalysts. We chose to use the reaction conditions (method A: benzene, reflux) employed by Doyle and co-workers.[3a]

As shown in Table 1, it is clear that in **1a**,**b**, the regioselectivity of the reaction is governed by the nature of the Rh(II) catalyst that is used. Thus, the strongly electron-withdrawing $Rh_2(pfb)_4$ favored insertion into the secondary C−H bond to give **4a**,**b** (entries 1 and 4). With $Rh_2(OAc)_4$ a reversal in the regioselectivity was observed; γ-lactone **5a**,**b**, resulting from preferential insertion into the tertiary C−H bond, was formed as the major product (entries 2 and 5). The reaction catalyzed by the "electronically selective"[3i] $Rh_2(acam)_4$ gave the highest yield of **5a,b** (entries 3 and 6). We found that the electron-withdrawing trifluoroethyl group of the ester moiety in **1b** had no influence on the reactivity of the metallocarbenoid; the ratio of products **4b**:**5b** mirrored those obtained for the Rh(II)-catalyzed reaction of **1a**.

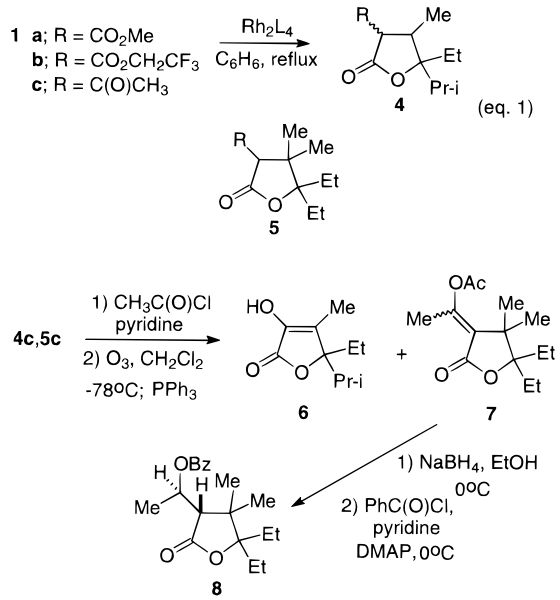
We also compared the regioselectivity of the reaction in **1c** to that in **1a**,**b**. It is interesting to note that substitution of the alkoxycarbonyl group with an acetyl substituent, as in **1c**, resulted in a marked decrease in the regioselectivity of the reaction. In particular, the use of $Rh_2(pfb)_4$ as the catalyst led to the exclusive formation of **4c** (entry 7).

Moreover, it is useful to compare the results from **1c** to the results reported by Doyle and co-workers on the regioselectivity for select α-diazoacetoacetates.[3a] Doyle and co-workers showed that the regioselectivity of the reaction is dependent on the structure of the compound.

Table 1. Rh(II)-Catalyzed Cyclization of 1 in Benzene at Reflux[a]

			γ-lactones **4**[c]:**5**		
entry	compound	catalyst	isolated yield,[b] %	relative yield, %	statistically corrected ratio
1	**1a**	$Rh_2(pfb)_4$	87	86:14	1.5:1
2	**1a**	$Rh_2(OAc)_4$	91	70:30	1:1.7
3	**1a**	$Rh_2(acam)_4$	90	42:58	1:5.5
4	**1b**	$Rh_2(pfb)_4$	78	86:14	1.5:1
5	**1b**	$Rh_2(OAc)_4$	79	73:27	1:1.5
6	**1b**	$Rh_2(acam)_4$	87	41:59	1:5.6
7	**1c**	$Rh_2(pfb)_4$	31	100:0	25:0
8	**1c**	$Rh_2(OAc)_4$	89	87:13[d]	1.8:1
9	**1c**	$Rh_2(acam)_4$	83	77:23[d]	1:1.2

[a] Final concentration of reaction mixture was 0.01 M. [b] Combined yield. [c] Compounds 4 were isolated as a mixture of diastereomers. [d] Compound 5c coeluted with **4c**. See Experimental Section for characterization of **4c** and **5c**. Ratio **4c**:**5c** was based on the integration of the MeCH multiplet (δ 3.06−3.15) in **4c** and the AcC*H*CO singlet (δ 3.30−3.50) in **5c**.



(eq. 1)

4

5

6

7

8

(6) (a) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522. (b) Clemens, R. J. *Chem. Rev.* **1986**, *86*, 241.
(7) Huston, R. S. *J. Am. Chem. Soc.* **1946**, *68*, 1382.
(8) Regitz, M. *Synthesis* **1972**, 381.
(9) Taber, D. F.; Ruckle, R. E., Jr.; Hennessy, M. J. *J. Org. Chem.* **1986**, *51*, 4077.
(10) Pfeffer, P. E.; Silbert, L. S.; Chirinko, J. M., Jr. *J. Org. Chem.* **1972**, *37*, 451.
(11) See Supporting Information.
(12) (a) Bates, H. A.; Rapoport, H. *J. Am. Chem. Soc.* **1979**, *101*, 1259. (b) Cox, M. T.; Jackson, A. H.; Kenner, G. W.; McCombie, S. W. *J. Chem. Soc., Perkin Trans 1* **1974**, 516.

Table 2. Rh(II)-Catalyzed Reaction of 2a,b

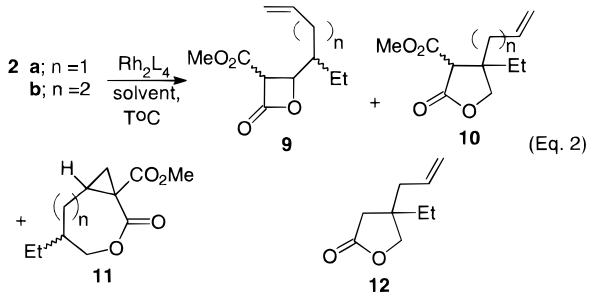
						relative yields, %		
entry	compound	catalyst	solvent	*T*, °C	yield, (%)[c]	**9**	**10**	**11**
1	**2a**	$Rh_2(OAc)_4$	CH_2Cl_2[a]	rt	92	11	55	34
2	**2a**	$Rh_2(OAc)_4$	CH_2Cl_2[a]	40	78	9.0	53	38
3	**2a**	$Rh_2(OAc)_4$	C_6H_6[a]	rt	66	<1	21	79
4	**2a**	$Rh_2(OAc)_4$	C_6H_6[a]	80	88	8.0	28	64
5	**2a**	$Rh_2(OAc)_4$	C_6H_6[b]	80	81	8.5	26	66
6	**2a**	$Rh_2(Oct)_4$	CH_2Cl_2[a]	rt	94	5.0	39	56
7	**2a**	$Rh_2(Piv)_4$	CH_2Cl_2[a]	rt	88	6.3	17	76
8	**2a**	$Rh_2(pfb)_4$	CH_2Cl_2[a]	rt	76	1.5	4.1	94
9	**2a**	$Rh_2(acam)_4$	CH_2Cl_2[a]	rt	80	nd[e]	29	60
10	**2a**	$Rh_2(Piv)_4$	C_6H_6[a]	rt	93	8.8	13	71
11	**2a**	$Rh_2(acam)_4$	C_6H_6[a]	rt	62	nd[e]	34	66
12	**2b**	$Rh_2(OAc)_4$	CH_2Cl_2[b]	40	87	11	84	6
13	**2b**	$Rh_2(Piv)_4$	CH_2Cl_2[b]	40	92	4.8	42	53
14	**2b**	$Rh_2(acam)_4$	CH_2Cl_2[b]	40	87	1	73	26
15	**2b**	$Rh_2(pfb)_4$	CH_2Cl_2[b]	40	65	19	13	68

[a] See Experimental Section: method A. [b] See Experimental Section: method B. Final concentration of mixture was 0.01 M. [c] Combined yield. [d] An inseparable mixture of diastereomers. [e] Not detected.

For example, they found that 2-methyl-3-isopropyl-3-heptyl-α-diazoacetoacetate[3a] was not responsive to the electronic influence of the Rh(II) catalyst; the predominant product formed was the γ-lactone that had resulted from insertion into a secondary C−H bond. It was suggested that the regioselectivity (tertiary *vs* secondary) was governed by conformational preferences in the compound. Compound **1c** can be considered a simplified analog of Doyle's 2-methyl-3-isopropyl-3-heptyl-α-diazoacetoacetate, but with one structural difference; the geminal substituents in the alkoxy moiety consist of an ethyl and isopropyl group. We found that the regioselectivity (tertiary *vs* secondary) in the reaction of **1c** was responsive, albeit small, to the nature of the Rh(II) catalysts employed. As alluded to earlier, the γ-lactone **4c** was the only product formed in the $Rh_2(pfb)_4$-catalyzed reaction. With $Rh_2(OAc)_4$, insertion into a tertiary C−H bond, to give **5c**, was competitive; however, the formation of **4c** was still preferred. The use of the "electronically selective"[3i] $Rh_2(acam)_4$ resulted in a preference for insertion into a tertiary C−H bond. These results suggest that in these systems, electronic effects transmitted to the metallocarbenoid site from the ligands in the dirhodium(II) catalyst as well as from the α-substituent on the carbenoid carbon govern the regioselectivity of the reaction.

Compounds **4c** and **5c** were obtained as an inseparable mixture. For further structural confirmation, the mixture was acetylated to give an inseparable mixture of enol acetates. This mixture was ozonized (CH_2Cl_2, −78 °C, 4 h) and then reduced to afford the crystalline α-tetronic acid **6** (from **4c**) and unoxidized, starting enol acetate **7** (contaminated by a small amount of an unidentified impurity). The resistance of **7** to ozonolysis was unexpected. This may be due to the steric shielding of the double bond in **7** by the vicinal *gem*-dimethyl groups which makes the double bond less accessible to attack by ozone. Treatment of **7** with $NaBH_4$ followed by benzoylation of the crude alcohol gave the benzoate derivative **8** as a single diastereomer (^{13}C NMR showed 19 lines). The salient signals in the ^1H NMR is the doublet due to H-3 which is centered at δ 2.96 ($J_{3,1'}$ = 9.8 Hz) and a double quartet due to the H-1′ which is centered at δ 5.45 ($J_{1',3}$ = 9.8 Hz and $J_{1',Me}$ = 5.6 Hz).

Having ascertained that the reactivity of the ester-substituted Rh(II) carbenoids can be modulated by the nature of the ligand on the dirhodium(II) metal center we then investigated the Rh(II) catalyzed reaction of compounds **2**. We began by examining the effect of solvent polarity[13] and reaction temperature on the regio- and chemoselectivities using compound **2a** as the test substrate, and $Rh_2(OAc)_4$ as the catalyst (eq 2). The



results are shown in Table 2.

It is apparent that solvent polarity affected the regio- and chemoselectivities of the reaction. The use of the more polar[14] CH_2Cl_2 resulted in a higher preference for the formation of γ-lactone **10a** over β-lactone **9a** (entries 1 and 2). However, the cyclopropanated lactone **11a**, which represented the second most abundant product, was also obtained. Although the reaction conducted in benzene[14] showed good regioselection, which is similar to that observed in CH_2Cl_2, there was a significant reversal in the chemoselectivity of the reaction. The cyclopropanated lactone **11a** was obtained as the major product and there was a marked decrease in the yield of **10a** (compare entries 1 and 3). Slow addition of a solution of **2a** in dry benzene to $Rh_2(OAc)_4$ in refluxing benzene did not improve on the yield of the γ-lactone **10a**; the ratio of the products was similar to those obtained under the usual conditions (compare entries 4 and 5). Reaction temperature had no effect on the regio- and chemoselectivities of the reaction (compare entries 1 and 2; 3 and 4).

The influence of the bridging ligands on the Rh(II) carbenoid-mediated reaction in **2a** was investigated. The reactions were conducted in CH_2Cl_2 at rt since the aforementioned studies indicated that the use of CH_2Cl_2

(13) For discussion on the dramatic influence of solvent polarity on the chemoselectivity of the Rh(II) carbenoid-mediated reaction, see (a) Davies, H. M. L.; Matasi, J. J.; Ahmed, G. *J. Org. Chem.* **1996**, *61*, 2305. (b) Davies, H. M. L.; Saikali, E.; Young, W. B. *J. Org. Chem.* **1991**, *56*, 5696 and references cited therein.

(14) Dielectric constant, ϵ, at 20 °C for CH_2Cl_2 = 9.08 and benzene = 2.284. Data from *CRC Handbook of Chemistry and Physics*, 76th ed.; Lide, D. R., Ed., **1995/1996**.

favored formation of the γ-lactone **10a**. In general, the results (Table 2, entries 6−9) show that the cyclopropanated lactone **11a** was the preferred product. The next most abundant product was the γ-lactone **10a**, and the β-lactone **9a** was again formed as a minor product. In the $Rh_2(acam)_4$-catalyzed reaction, **9a** was not detected (entry 9). In particular, the $Rh_2(pfb)_4$-catalyzed reaction afforded the cyclopropanated lactone **11a** as the predominant product. It is also useful to compare the results from the Rh(II) carboxylate-catalyzed reaction in **2a** (entries 1, 6, and 7); the highest yield recorded for the γ-lactone **10a** was that from the $Rh_2(OAc)_4$-catalyzed reaction whereas the $Rh_2(Oct)_4$ and $Rh_2(Piv)_4$[15] mediated reactions resulted in a marked decrease in the yield of **10a** but a paralleled increase in the yield of **11a**. In addition, it was noted that the reaction of **2a** with $Rh_2(OAc)_4$ in benzene at rt resulted in a good yield (79%) of **11a** (entry 3, Table 2). It was also evident that formation of **11a** was favored when the more soluble $Rh_2(Piv)_4$ and $Rh_2(acam)_4$ catalysts were used (entries 7 and 9). Therefore, we investigated the $Rh_2(Piv)_4$- and $Rh_2(acam)_4$-catalyzed reactions of **4a** in benzene to see whether a higher yield of **11a** could be realized. Disappointingly, these modified conditions did not lead to any improvement in the yield of **11a** (compare entries 7 and 10; 9 and 11).

On the basis of the above results, we surmised that tertiary C−H insertion (γ-lactone formation) and cyclopropanation are the two energetically favorable and competing pathways; the minor, energetically more demanding pathway is secondary C−H insertion, which results in the formation of the strained β-lactone product. We reasoned that the cyclopropanation pathway would become less competitive, based on enthalpic and entropic considerations, if the double-bond was moved one additional carbon farther from the metallocarbenoid center. This, in turn, should result in a higher preference for tertiary C−H insertion. To test this hypothesis, we examined the Rh(II) catalyzed reaction of compound **2b** (homolog of **2a**).[16]

We found that the reaction was best performed by the slow addition (syringe pump) of a CH_2Cl_2 solution of **2b** to the Rh(II) catalyst in refluxing CH_2Cl_2. This procedure suppresses the formation of dimeric byproducts and good overall yields of products were obtained (eq 2). As shown in Table 2 (entries 12−15), the β-lactone **9b** was again formed as the minor product with one exception; the $Rh_2(pfb)_4$-catalyzed reaction (entry 15) produced almost a 1.4:1 ratio of **9b**:**10b**. It is clear that lengthening of the carbon chain did not completely "shut-down" cyclopropanation of the double bond. The use of $Rh_2(pfb)_4$ resulted in the highest yield of the eight-membered lactone **11b** but at the expense in the yield of **10b** (entry 15). Among the four Rh(II) catalysts examined, the best yield of the γ-lactone **10b** was realized with $Rh_2(OAc)_4$ as the catalyst (entry 12). The use of the "bulky" $Rh_2(Piv)_4$ resulted in a modest yield of **10b**. However, when this result is compared to that obtained for **2a** (entry 7), it is apparent that the yield of **11b** has decreased significantly, but this was accompanied by a proportionate increase in the yield of **10b** (compare entries 7 and 10: **10a**:**11a** = 1:4.5; **10b**:**11b** = 1:1.2). With $Rh_2(acam)_4$ a good yield of **10b** was obtained (entry 14). In comparing this result with that obtained for **2a**, it is evident that there is a significant reversal in the chemoselectivity of the reaction (compare entries 14 and 9).

Each of the products **9**−**11** was obtained as a mixture of diastereomers; in general, compounds **9**, **10**, and **11** were separable by flash chromatography. In the case of the Rh(II)-catalyzed reaction of **2a**, with the exception of the $Rh_2(pfb)_4$ reaction, a minor, unidentified component coeluted with **11a**, and further attempts at the chromatographic purification of **11a** were unsuccessful. However, it was found that treatment of the mixture of **11a** and the minor component with aqueous DMSO containing NaCl[17] at 130 °C resulted, unexpectedly, in the selective destruction of the minor impurity and recovery of **11a** (50%).

The structures of compounds **9** and **10** were readily assigned based on their spectroscopic data. For example, compounds **9** exhibited a strong infrared absorption in the range 1844−1845 cm^{-1} that is characteristic of the β-lactone carbonyl group. The salient features in the ^1H NMR of **9** is the H-3 doublet in the region δ 4.19−4.20. This doublet has a small vicinal coupling constant ($J_{3,4}$) of 3.7−4.9 Hz, which is indicative of a *trans*[18] relative stereochemistry between the C-3 alkoxycarbonyl and C-4 alkyl substituents. The H-4 signal resonated as an apparent quintet in the region δ 4.60−4.70. In **10**, the γ-lactone carbonyl absorbed in the range 1784−1788 cm^{-1} and the diagnostic features in their ^1H NMR are the H-3 singlets that resonated at δ 3.30 and δ 3.33, and the C-5 methylenes which resonated in the region between δ 4.02 and 4.24. It is noteworthy that in **10a** (1:1 mixture of diastereomers) the C-5 methylenes were observed as two sets of doublets; in the first set, one doublet is centered at δ 4.02 and the other at δ 4.24. In the second set, one doublet is centered at δ 4.10 and the other at δ 4.20. In comparison, the C-5 methylenes in **10b** (1:1 mixture of diastereomers) resonated only as a set of doublets, one centered at δ 4.10 and the other at δ 4.22. It is likely that in **10a**, the double bond in the 3-(2-propenyl) group may be positioned close to the C-5 methylene hydrogens. The anisotropic effect of the double bond causes each of the hydrogens in the methylene groups of each diastereomer to resonate at a different chemical shift. The structure of **10a** was further confirmed by conversion, via decarboxylation,[17] to give **12**. Its ^1H NMR showed the absence of the H-3 singlet and the presence of two new doublets, one centered at δ 2.28 and the other centered at δ 2.39. The C-5 methylenes also simplified to two doublets.

The diastereomeric mixture of each of the cyclopropanated lactones **11a**,**b** that were obtained from the $Rh_2(pfb)_4$-catalyzed reaction of **2a,b** were used for structural assignment. A combination of 1D and 2D NMR techniques were used. Because **11a** was obtained as a

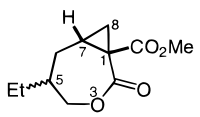
(15) (a) Reference 4a; Ikegami and co-workers showed that $Rh_2(Piv)_4$ favored insertion into tertiary C−H bond. (b) $Rh_2(Piv)_4$ was also found to favor cyclopropanation reaction, see (i) Sundberg, R. J.; Baxter, E. W.; Pitts, W. J.; Ahmed-Schofield, R.; Nishiguchi, T. *J. Org. Chem.* **1988**, *53*, 5097. (ii) Anciaux, A. J.; Hubert, A. J.; Noels, A. F.; Petiniot, N.; Teyssie, P. *J. Org. Chem.* **1980**, *45*, 695. (iii) Hubert, A. J.; Noels, A. F.; Anciaux, A. J.; Teyssie, P. *Synthesis* **1976**, 600.

(16) Diazo compounds in which the ethyl group in **2a**,**b** was replaced with a 3,4-dimethoxyphenyl moiety were also prepared. The Rh(II)-catalyzed reaction in **2a** resulted in an intractable mixture of products whereas in **2b** there was a marked decrease in the regio- and chemoselectivities of the reaction. A complex mixture of products, such as those that had resulted from tertiary C−H insertion, aromatic substitution and cycloaddition, were obtained.

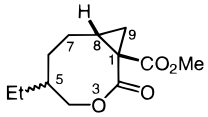
(17) Krapcho, A. P. *Synthesis* **1982**, 805, 893.

(18) (a) Mulzer, J.; Zippel, M.; Bruntrup, G.; Segner, J.; Finke, J. *Liebigs Ann. Chem.* **1980**, 1108. (b) Mulzer, J.; Pointner, A.; Chucholowski, A.; Bruntrup, G. *J. Chem. Soc., Chem. Commun.* **1979**, 52.

Table 3. ^{13}C Resonances of Cyclopropanated Lactones 11a-A, 11a-B and 11b-A, 11b-B



11a-A, 11a-B



11b-A, 11b-B

entry	carbon	**11a-A**	**11a-B**	carbon	**11b-A**	**11b-B**
1	Me	11.45	11.72	Me	11.98	11.35
2	C-8	22.42	21.86	C-9	21.46	21.12
3	C-7	23.76	20.37	CH_2	26.72	22.36
4	CH_2	26.29	22.87	C-7	27.97	24.44
5	C-1	31.12	31.61	C-8	30.22	31.16
6	C-6	32.07	29.89	C-1[a]	32.56	32.57
7	C-5	37.89	36.59	C-6	34.18	32.28
8	OMe	52.92	52.89	C-5	42.07	39.50
9	C-4	69.21	70.29	OMe[a]	52.92	52.88
10	C-2	169.19	169.24	C-4	73.52	70.46
11	CO_2Me	170.08	169.98	C-2[a]	169.75	169.23
12	–	–	–	CO_2Me	170.45	170.45

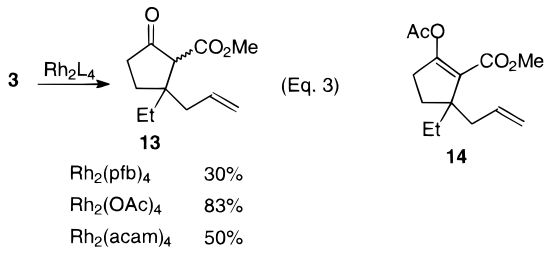
[a] Carbon signals may be interchanged.

mixture of two diastereomers (3.5:1), we have used the designation **11a-A** and **11a-B** to indicate the major and minor diastereomer, respectively. For **11b**, the two diastereomers were formed in equal amounts; one of the diastereomers is designated **11b-A** and the other as **11b-B**. Proton assignments were confirmed by 2D-COSY-45 experiments;[19] in the case of **11b**, 1D-TOCSY experiments[20] were also conducted to obtain the ^{1}H NMR spectrum for the region between δ 0.70−2.50. ^{13}C assignments were obtained from 2D-HSQC experiments.[21] As well, further information on the resonances of select groups of protons that are attached to the carbons in each of the diastereomers were extracted from rows in the 2D-HSQC matrix. The ^{13}C resonances for the individual isomers of **11a** and **11b** are collected in Table 3.

The common features in the ^{1}H NMR spectra in **11a**,**b** were the signals due to the C-4 methylene hydrogens which appeared in the region between δ 4.05−4.60, and the C-5 methine hydrogen which was found in the region between δ 1.62−2.02. The other pertinent signals that are characteristic for **11a**,**b** are summarized in Table 4. It is useful to note that in compounds **11a** and **11b**, the resonance for each of the methylene hydrogens that are adjacent to the ring juncture hydrogen in each diastereomer (i.e., **11a-A** and **11a-B**; **11b-A** and **11b-B**) are well separated by more than 1.1 ppm. For the cyclopropyl CH_2 unit, the signal of each of the hydrogens in each diastereomer showed a smaller separation; in the **11a** pair, the separation is 0.6 ppm and for the **11b** pair, it is 0.35 ppm.

We were not able to assign the relative stereochemistry of the ethyl group with respect to the cyclopropyl moiety in each of the diastereomers in **11a**,**b**; NOE experiments conducted on **11a** were inconclusive.

We also briefly investigated the Rh(II)-catalyzed reaction in the α-diazo-*β*-keto ester system **3** (eq 3, method A). Diazo compound **3** can be considered as the "carbon" analog of **2a** and, therefore, it is instructive to compare the results with those obtained from **2a**. Both the Rh_2(OAc)$_4$- and Rh_2(pfb)$_4$-catalyzed reaction furnished a



mixture that comprised of a less polar (R_f = 0.50, 7:1 PE:Et$_2$O) and more polar (R_f = 0.28, 7:1 PE:Et$_2$O) components, whereas with Rh_2(acam)$_4$ only the less polar component was obtained. The less polar component was identified as the substituted cyclopentanone **13** that resulted from insertion into the tertiary C−H bond,[22] and which existed as a mixture of keto and enol tautomers. For further corroboration of structure, **13** was acetylated to afford the enol acetate **14**.

As expected, Rh_2(OAc)$_4$-promoted insertion into the tertiary C−H bond and a good yield (83%) of **13** was obtained. On the other hand, Rh_2(pfb)$_4$ gave the lowest yield (30%) of **13**. The more polar component showed a very complex ^{1}H NMR which hampered further structural characterization. Nevertheless, the presence of the double-bond resonances (δ 4.95−5.10, =CH$_2$ and δ 5.65−5.90, =CH) indicated that cyclopropanation was not a favored pathway in the reaction of **3**. As far as yields of the tertiary C−H insertion products are concerned, these results indicate that the response of **3** to the different Rh(II) catalysts follows a trend similar to that observed in **2a**. More importantly, in comparing the results of **2a** and **3**, it is very clear that the ester oxygen atom in **2a** plays an important role in influencing the regio- and chemoselectivities of the reaction.

Discussions

Although the results obtained from the Rh(II)-catalyzed reaction of **1a**−**c** revealed that the regioselectivity of the reactions was generally responsive to the nature of the catalyst used, it is useful to note that the nature of the α-substituent on the metallocarbenoid carbon also has an influence on the outcome of the reaction. In the ester series, **1a**,**b**, it was found that insertion into the tertiary C−H bond was the preferred pathway regardless of the *O*-alkyl substituent (OMe *vs* OCH_2CF_3) when the reactions were catalyzed by Rh_2(OAc)$_4$ and Rh_2(acam)$_4$. The latter catalyst gave the best regioselection (tertiary ≫ secondary). The regioselectivity decreased when the α-substituent is the acetyl unit; with Rh_2(OAc)$_4$, insertion into secondary and tertiary C−H bonds was competitive whereas with Rh_2(acam)$_4$ there was a small preference for insertion into the tertiary C−H bond. With Rh_2(pfb)$_4$, insertion into the secondary C−H bond was preferred in **1a**,**b**, but was the exclusive pathway in **1c**.

These results indicate that the electronic effect of the substituent on the carbenoid carbon also exerts an important although subtle influence on the electrophilicity of the Rh(II) carbenoid site. We[23] and others[24] have previously suggested that the α-substituent located on the carbenoid carbon can influence the chemoselectivity

(19) Aue, W. p.; Bartoldi, E.; Ernst, R. R. *J. Chem. Phys.* **1976**, *64*, 2229. (b) Bax, A.; Freeman, R. *J. Magn. Reson.* **1981**, *44*, 542.

(20) Braunschweiler, L.; Ernst, R. R. *J. Magn. Reson.* **1983**, *53*, 521. (b) Davis, D. G.; Bax, A. *J. Am. Chem. Soc.* **1985**, *107*, 2820.

(21) Maudsley, A. A.; Ernst, R. R. *Chem. Phys. Lett.* **1977**, *50*, 368.

(22) For a similar tertiary C−H insertion in α-diazo-α-phenylsulfonyl ketones, see Monteiro, H. J.; Zuckerman-Schpector, J. *Tetrahedron* **1996**, *52*, 3879.

(23) Wee, A. G. H.; Liu, B.-S.; Zhang, L. *J. Org. Chem.* **1992**, *57*, 4404.

Table 4. Select (δ 0.50−2.50) ^{1}H Resonances for Compounds 11a,b

	δ, multiplicity, J (Hz)				
proton	**11a-A**	**11a-B**	proton	**11a-A**	**11a-B**[b]
H-6	0.55; dq; 16.8, 10	0.92−0.98, m	H-7	0.86; dq; 14.7, 12.0	0.94−0.99; m
H6′	2.41; dt; 16.8, 5.0	2.25; dd; 15.1, 3.7	H-7′	2.34; ddd; 14.7, 8.3, 2.0	2.10−2.18; m
H-7	1.62−1.73; m[a]	1.61−1.72; m[a]	H-8	1.80−1.88; m	1.83−1.91; m
H-8	1.13; t; 4.5[a]	1.10; t; 4.5[a]	H-9	1.22−1.32; m	1.25; dd; 7.2, 4.7
H-8′	1.73; dd, 8.1, 4.5[a]	1.71; dd; 8.1, 4.5[a]	H-9′	1.60; dd; 8.3, 4.2	1.57; dd; 8.8, 4.7

[a] Data was extracted from rwos in the 2D-HSQC matrix. [b] Data was obtained from 1D-TOCSY spectra of the individual isomers.

of the metallocarbenoid. It is reasonable to suggest that the acetyl substituent is a stronger electron-withdrawing group than the ester function,[23] which would cause the acetyl-substituted metallocarbenoid to be more electrophilic. Because of its enhanced electrophilicity, the metallocarbenoid is more reactive and, therefore, less selective (early transition state).[3a] Consequently, this would result in lower regioselectivity in the C−H insertion reaction.

For the β'-branched systems, **2a**,**b**, C−H insertion and cycloaddition to the alkene double bond were identified as two competitive reaction pathways that were available for the reactive, transient metallocarbenoid intermediate. It should be noted that dirhodium(II) carbenoid-mediated intramolecular cyclopropanation reactions generally favor formation of bicyclo[3.1.0]hexane and bicyclo[4.1.0]-heptane ring systems.[1,25] The formation of lower or higher homologs of these ring systems are uncommon. The formation of the 3-oxabicyclo[5.1.0] and 3-oxabicyclo-[6.1.0] lactones, **11a** and **11b**, was unexpected and suggests that their formation may be entropically favored.

As far as the regioselectivity [tertiary (γ-lactone) *vs* secondary (β-lactone)] of the reaction is concerned, Rh_2-$(OAc)_4$ was the catalyst of choice for promoting insertion into a tertiary C−H bond; the next best catalyst was Rh_2-$(acam)_4$. The chemoselectivity of the reaction in **2a**,**b** was governed mainly by the nature of the Rh(II) catalyst as well as the steric size of the ligand in the dirhodium(II) core, and to a smaller extent the polarity of the solvent (CH_2Cl_2 *vs* benzene). For example, the $Rh_2(OAc)_4$-catalyzed reaction of **2a** in CH_2Cl_2 gave the tertiary C−H insertion product **10a** as the major product; the second most abundant product was the cyclopropanated lactone **11a**. The same reaction in benzene, however, afforded **11a** as the major product. More importantly, amongst the three rhodium(II) carboxylates used in the studies $Rh_2(Oct)_4$- and $Rh_2(Piv)_4$-promoted cycloaddition of the alkene double bond with the latter catalyst providing the highest yield of cycloaddition product **11a**,**b**. We attribute the decrease in the yield of γ-lactone **10a** or **10b** in going from $Rh_2(OAc)_4$ to $Rh_2(Oct)_4$ to $Rh_2(Piv)_4$ to an increase in steric size of the metallocarbenoid, which makes tertiary C−H insertion more difficult. As a result, the metallocarbenoid reacts via the next least energetically demanding pathway, namely, cyclopropanation to give compounds of type **11**. In the case of the electron-donating $Rh_2(acam)_4$, cyclopropanation of the double bond was the major pathway observed in the reaction of **2a**; this pathway was still significant in the reaction of **2b**. This outcome is in general agreement with the observation that amide-based ligands[3b,26] on the dirhodium(II) metal promote cyclopropanation over tertiary C−H insertion. The optimal conditions for effecting intramolecular cyclopropanation in compounds of type **2** are the use of $Rh_2(pfb)_4$ as catalyst and CH_2Cl_2 as solvent.

In summary, we found that ester-substituted Rh(II) carbenoids are responsive to the electronic nature of the ligand on the dirhodium(II) metal. We also found that the nature of the alkyl moiety in the α-(alkoxycarbonyl) substituent in compounds of type **1** had no influence on the regioselectivity of the reaction. The regio- and chemoselectivities in the reaction of β'-branched *O*-alkyl-α-(alkoxycarbonyl)-α-diazoacetates can be controlled via the use of the appropriate Rh(II) catalyst. In particular, $Rh_2(OAc)_4$ was found to promote tertiary C−H insertion in compounds of type **2**, resulting in the formation of 4,4-disubstituted-γ-lactone **10** as the major product. Interestingly, intramolecular cyclopropanation of the double bond was found to be a competitive pathway. $Rh_2(pfb)_4$, in particular, was found to promote cyclopropanation of the double bond over C−H insertion. The Rh(II)-catalyzed reaction of **3** ("carbon" analog of **2a**) resulted mainly in the cyclopentanone derivative **13**, and no cyclopropanation product was detected. This result indicates that the ester oxygen in compounds of type **2** plays an important role in influencing the regio- and chemoselectivities of their reaction. For diazo compounds of a particular type of structure the regio- and chemoselectivities of the reaction can be controlled via the judicious choice of the Rh(II) catalyst. The results reported here are useful in the planning of Rh(II) carbenoid C−H insertion approaches in target-directed synthesis.

Experimental Section

Only diagnostic absorptions in the infrared spectrum are reported. ^{1}H (200 MHz) and ^{13}C (50.32 MHz) NMR spectra were recorded in $CDCl_3$ unless otherwise stated. Tetramethylsilane ($\delta_H = 0.00$) and the $CDCl_3$ resonance ($\delta_C = 77.0$) were used as references. In the ^{13}C DEPT-135 experiment[27] the inverted signals of the CH_2s are designated (−). Elemental analyses and high resolution electron impact (70 eV) and chemical ionization mass spectral analyses were performed at the Chemistry Department, University of Saskatchewan, Canada. Reaction progress was monitored by thin-layer

(24) (a) Ceccherelli, P.; Curini, M.; Marcotullio, M. C.; Rosati, O. *Tetrahedron* **1992**, *48*, 9767. (b) Doyle, M. P.; Shanklin, M. S.; Oon, S.-M.; Pho, H. Q.; van der Heide, F. R.; Veal, W. R. *J. Org. Chem.* **1988**, *53*, 3384. (c) Doyle, M. P.; Shanklin, M. S.; Pho, H.-Q.; Mahapatro, S. N. *J. Org. Chem.* **1988**, *53*, 1017.

(25) (a) For a review: Doyle, M. P. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 305. (b) Padwa, A. *Tetrahedron Lett.* **1993**, *34*, 4285. (c) Doyle, M. P.; Austin, R. E.; Bailey, A. S.; Dwyer, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Kwan, M. M. Y.; Liras, S.; Oalman, C. J.; Pieters, R. J.; Protopopova, M. N.; Raab, C. E.; Roos, G. H. P.; Zhou, Q.-L.; Martin, S. F. *J. Am. Chem. Soc.* **1995**, *117*, 5763. (d) Doyle, M. P.; Zhou, Q.-L. *Tetrahedron: Asymmetry* **1995**, *6*, 2157. For an exception, see Doyle, M. P.; Protopopova, M. N.; Poulter, C. D.; Rogers, D. H. *J. Am. Chem. Soc.* **1995**, *117*, 1281.

(26) (a) Doyle, M. P.; Bagheri, V.; Wandless, T. J.; Ham, N. K.; Brinker, D. A.; Eagle, L. T.; Loh, K.-L. *J. Am. Chem. Soc.* **1990**, *112*, 1906. (b) Doyle, M. P.; Loh, K.-L.; Devries, K. M.; Chinn, M. S. *Tetrahedron Lett.* **1987**, *28*, 833.

(27) Doddrell, D. M.; Pegg, D. T.; Bendall, M. R. *J. Magn. Reson.* **1982**, *48*, 323.

chromatography on Merck silica gel 60_{F254} precoated (0.25 mm) on aluminum-backed sheets. Air and moisture sensitive reactions were conducted under a static pressure of argon. All organic extracts were dried over anhydrous Na_2SO_4. Flash chromatography[28] was performed on Merck silica gel 60 (230−400 mesh). Unless otherwise indicated, the eluent is either a mixture of petroleum ether (PE, bp 35−60 °C) and ethyl acetate (EtOAc) or a mixture of petroleum ether and diethyl ether (Et_2O). Rhodium(II) acetate [$Rh_2(OAc)_4$] and rhodium(II) octanoate [$Rh_2(Oct)_4$] were purchased from Strem Chemicals Inc., (Newburyport, MA) and dried under high vacuum (0.05 Torr) at 100 °C before use. Rhodium(II) acetamide [$Rh_2(acam)_4$],[26a] rhodium(II) pivalate [$Rh_2(Piv)_4$],[29] and rhodium(II) perfluorobutyrate [$Rh_2(pfb)_4$][30] were prepared according to literature procedures.

General Procedure for the Diazotization. The appropriate malonate or β-keto ester (0.1 mmol) was dissolved in dry MeCN at 0 °C. MsN_3[9] was added followed by addition of DBU (0.2 mmol) dropwise. The mixture was stirred at 0 °C for 30 min then at rt for 3 h. The mixture was diluted with CH_2Cl_2 and washed with 10% aqueous NaOH and water. The aqueous layer was reextracted with more CH_2Cl_2. The combined CH_2Cl_2 layers were dried (Na_2SO_4), filtered, and concentrated. The crude diazo compounds **1**−**3** were purified by flash chromatography.

Methyl 3-ethyl-2-methyl-3-pentyl-α-diazomalonate (1a). 20:1 and then 7:1 PE:Et_2O. Yield: 92%. IR υ_{max} (neat): 2134, 1765, 1742, 1687 cm^{-1}. ^{1}H NMR, δ: 0.90 (t, 6H, J = 8.0 Hz), 0.93 (d, 6H, J = 6.9 Hz), 1.92 (q, 2H, J = 8.0 Hz), 1.93 (q, 2H, J = 8.0 Hz), 2.38 (septet, 1H, J = 6.9 Hz), 3.81 (s, 3H). ^{13}C NMR, δ: 8.9, 17.7, 27.3 (−), 34.2, 52.4, 93.4, 159.5, 164.2. Anal. Calcd for $C_{12}H_{20}N_2O_4$: C, 56.23; H, 7.87; N, 10.93. Found: C, 56.10; H, 7.61; N, 10.68.

2,2,2-Trifluoroethyl 3-Ethyl-2-methyl-3-pentyl-α-diazomalonate (1b). 20:1 and then 7:1 PE:Et_2O. Yield: 59%. IR υ_{max} (neat): 2142, 1766, 1690 cm^{-1}. ^{1}H NMR, δ: 0.93 (t, 6H, J = 7.6 Hz), 0.96 (d, 6H, J = 6.6 Hz), 1.95 (q, 2H, J = 8.0 Hz), 1.96 (q, 2H, = 8.0 Hz), 2.42 (septet, 1H, J = 7.0 Hz), 4.60 (q, 2H, $J_{H,F}$ = 8.0 Hz). ^{13}C NMR, δ: 8.8, 17.7, 27.2 (−), 34.2, 60.4 (−), 94.3, 158.7, 159.5. Anal. Calcd for $C_{13}H_{19}N_2O_4$: C, 48.14; H, 5.90; N, 8.64. Found: C, 48.05; H, 5.83; N, 8.58.

3-Ethyl-2-methyl-3-pentyl α-diazoacetoacetate (1c). 20:1 and then 7:1 PE:Et_2O. Yield: 75%. IR υ_{max} (neat): 2128, 1712, 1660 cm^{-1}. ^{1}H NMR, δ: 0.91 (t, 6H, J = 7.4 Hz), 0.94 (d, 6H, J = 6.8 Hz), 1.93 (q, 2H, J = 7.4 Hz), 1.94 (q, 2H, J = 7.4 Hz), 2.39 (septet, 1H, J = 6.8 Hz), 2.43 (s, 3H). ^{13}C NMR, δ: 8.9, 17.7, 27.3 (−), 28.1, 34.4, 93.5, 160.2. Anal. Calcd for $C_{12}H_{20}N_2O_3$: C, 59.98; H, 8.39; N, 11.66. Found: C, 59.74; H, 8.22; N, 11.46.

Methyl 2-Ethyl-4-pentenyl-α-diazomalonate (2a). 7:1 PE:Et_2O. Yield: 90%. IR υ_{max} (neat): 2136, 1766, 1738, 1698 cm^{-1}. ^{1}H NMR, δ: 0.94 (t, 3H, J = 7.4 Hz), 1.38 (quint, 2H, J = 6.9 Hz), 1.73 (septet, 1H, J = 6.3 Hz), 2.12 (t, 2H, J = 6.3 Hz), 3.86 (s, 3H), 4.18 (d, 2H, J = 5.1 Hz), 4.98−5.10 (m, 2H), 5.67−5.87 (m, 1H). ^{13}C NMR, δ: 11.1, 23.4 (−), 35.1 (−), 36.8, 52.5, 67.3 (−), 116.7 (−), 135.9, 160.9, 161.6. Anal. Calcd for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66. Found: C, 54.73; H, 6.46; N, 11.69.

Methyl 2-Ethyl-5-hexenyl-α-diazomalonate (2b). 20:1 and then 7:1 PE:Et_2O. Yield: 86%. IR υ_{max} (neat): 2136, 1764, 1738, 1698 cm^{-1}. ^{1}H NMR, δ: 0.91 (t, 3H, J = 7.4 Hz), 1.31−1.50 (m, 4H), 1.68 (septet, 1H, J = 6.7 Hz), 2.08 (br q, 2H, J = 8.0 Hz), 3.83 (s, 3H), 4.18 (d, 2H, J = 5.7 Hz), 4.91−5.09 (m, 2H), 5.69−5.90 (m 1H). ^{13}C NMR, δ: 10.9, 23.6 (−), 29.9 (−), 30.9 (−), 38.2, 52.5, 67.5 (−), 114.7 (−), 138.5, 160.9, 161.6. HRMS calcd for $C_{12}H_{18}N_2O_4 + H^+$ 255.1345, found 255.1336.

Methyl 2-Diazo-6-ethyl-3-oxo-8-nonenoate (3). 20:1 and then 7:1 PE:Et_2O. Yield: 84%. IR υ_{max} (neat): 2135, 1727, 1659 cm^{-1}. ^{1}H NMR, δ: 0.88 (t, 3H, J = 7.1 Hz), 1.21−1.50 (m, 3H), 1.55−1.68 (m, 2H), 2.05 (t, 2H, J = 6.4 Hz), 2.85 ("t", 2H, J = 7.8 Hz), 3.84 (s, 3H), 4.95−5.08 (m, 2H), 5.65−5.89 (m, 1H). ^{13}C NMR, δ: 10.79, 25.48 (−), 27.39 (−), 37.54 (−), 37.71 (−), 38.54, 52.11, 115.94 (−), 136.96, 161.77, 193.07.

General Procedure for the Rh(II)-Catalyzed Reaction of Diazo Compounds 1−3. Method A. The diazo compound (0.5 mmol) was dissolved in 50 mL of either dry CH_2Cl_2 or benzene. Then the appropriate Rh(II) catalyst (2 mol %) was added. The mixture was stirred either at rt or at reflux. After 20 h, the mixture was filtered (for reactions conducted at reflux, the mixture was first cooled to rt before being processed), and concentrated, and the residual oil was flash chromatographed to obtain the products.

Method B. The diazo compound (0,5 mmol) was dissolved in 30 mL of either dry CH_2Cl_2 or benzene, and the solution was added dropwise, using a syringe pump, over a period of 6 h to the Rh(II) catalyst (2 mol %) in 20 mL of the appropriate solvent at reflux (see Table 2). After addition was complete, the mixture was stirred at reflux for 20 h. The mixture was cooled to rt, filtered, concentrated and flash chromatographed to give the products.

5-Ethyl-5-isopropyl-3-(methoxycarbonyl)-4-methyldihydro-2(3*H*)-furanone (4a). Mixture of diastereomers. IR υ_{max} (neat): 1774, 1740 cm^{-1}. ^{1}H NMR, δ: 0.90−1.05 (m, 9H), 1.17 and 1.23 (d, 3H, J = 7.2 Hz), 1.50−2.30 (m, 3H), 2.90−3.10 (m, 1H), 3.36 (d, J = 12.0 Hz) and 3.45 (d, J = 12.6 Hz)(1H), 3.82 and 3.84 (s, 3H). Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.09; H, 8.98.

5-Ethyl-5-isopropyl-4-methyl-3-(2,2,2-trifluoroethoxycarbonyl)dihydro-2(3*H*)-furanone (4b). Mixture of diastereomers. IR υ_{max} (neat): 1778, 1754 cm^{-1}. ^{1}H NMR, δ: 0.95−1.04 (m, 9H), 1.19 and 1.24 (d, 3H, J = 6.3 Hz), 1.50−2.32 (m, H), 2.90−3.10 (m, 1H), 3.45 and 3.55 (d, 1H, J = 12.0 Hz), 4.40−4.76 (m, 2H). Anal. Calcd for $C_{13}H_{19}F_3O_4$: C, 52.70; H, 6.46. Found: C, 52.74; H, 6.36.

5,5-Diethyl-3-(methoxycarbonyl)-4,4-dimethyldihydro-2(3*H*)-furanone (5a). IR υ_{max} (neat): 1780, 1735 cm^{-1}. ^{1}H NMR, δ: 0.92 (t, 3H, J = 7.4 Hz), 0.96 (t, 3H, J = 7.4 Hz), 1.09 (s, 3H), 1.27 (s, H), 1.50−2.00 (m, 4H), 3.55 (s 1H), 3.77 (s, 3H). ^{13}C NMR, δ: 8.00, 8.60, 20.9, 23.6, 24.3 (−), 25.0 (−), 45.7, 52.4, 58.0, 91.6, 167.5, 170.6. Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.09; H, 9.02.

5,5-Diethyl-4,4-dimethyl-3-[(2,2,2-trifluoroethoxy)carbonyl]dihydro-2(3*H*)-furanone (5b). IR υ_{max} (neat): 1790, 1750 cm^{-1}. ^{1}H NMR, δ: 0.95 (t, 3H, J = 7.4 Hz), 1.00 (t, 3H, J = 7.4 Hz), 1.13 (s, 3H), 1.31 (s, 3H), 1.50−2.10 (m, 4H), 3.68 (s, 1H), 4.30−4.50 (m, 1H), 4.60−4.80 (m 1H). ^{13}C NMR, δ: 8.00, 8.60, 20.7, 23.3, 24.2 (−), 25.0 (−), 46.0, 57.6, 61.1 (q, -), 91.8, 119.9, 125.9, 165.5, 169.6. Anal. Calcd for $C_{13}H_{19}F_3O_4$: C, 52.70; H, 6.46. Found: C, 52.95; H, 6.62.

3-Acetyl-5-ethyl-5-isopropyl-4-methyldihydro-2(3*H*)-furanone (4c) and 3-Acetyl-5,5-diethyl-4,4-dimethyldihydro-2(3*H*)-furanone (5c). Compound **5c** coeluted with **4c**. Spectroscopic data is reported for the mixture. IR υ_{max} (neat): 1744 cm^{-1}. ^{1}H NMR, δ: 0.85−1.25 (m, 12H), 1.50−2.35 (m H), 2.33 and 2.42 (s, H), 3.00−3.15 (m, 1H), 3.38 and 3.47 (d, 1H, J = 11.7 Hz). The presence of **5c** was evidenced by the singlet at δ 3.36 attributed to MeC(O)C*H*C(O) unit. Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.75; H, 9.51.

Characterization of 4c and 5c. The mixture of **4c** and **5c** (170 mg, 0.810 mmol) was dissolved in dry pyridine (4 mL) and was treated with acetyl chloride (0.09 mL, 1.20 mmol) to give an inseparable mixture of the corresponding enol acetates (140 mg, 69%). Without further processing, the enol acetates were dissolved in dry CH_2Cl_2 (10 mL) and cooled to −78 °C. Ozone was bubbled into the solution for 4 h, and then argon was bubbled into the solution to drive off excess ozone. Ph_3P (10 mg, 0.572 mmol) was added, and the mixture was stirred at rt overnight. CH_2Cl_2 was evaporated, and the residual oil was chromatographed to furnish the α-tetronic acid **6** (27 mg). Unoxidized enol acetate **7** (17 mg) was also recovered, but was contaminated with a small amount of an unidentified component.

α-Tetronic Acid 6. IR υ_{max} (neat): 3525−3100, 3068, 1735, 1708 cm^{-1}. ^{1}H NMR δ: 0.70 (t, 3H, J = 7.4 Hz), 0.78 (d, 3H, J = 6.8 Hz), 1.50 (d, 3H, J = 6.8 Hz), 1.55−1.75 (m, 1H), 1.82

(28) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(29) Cotton, F. A.; Felthouse, T. R. *Inorg. Chem.* **1980**, *19*, 323.
(30) Doyle, M. P.; Mahapatro, S. N.; Caughey, A. C.; Chinn, M. S.; Colsman, M. R.; Hain, H. K.; Redwine, A. E. *Inorg. Chem.* **1987**, *26*, 3070.

(s, 3H), 1.90−2.04 (m, 1H), 2.05-.22 (m, 1H), 6.45 (s, 1H). ^{13}C NMR δ: 7.00, 9.29, 16.58, 26.57, 33.50, 91.66, 133.33, 137.99, 170.73. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.95; H, 8.55.

Recovered Enol Acetate 7. IR υ_{max} (neat): 1760, 1748, 1681 cm^{-1}. ^{1}H NMR δ: 0.95 (t, 3H, J = 7.4 Hz), 0.97 (t, 3H, J = 7.4 Hz), 1.22 (s, 3H), 1.26 (s, 3H), 1.62−1.80 (m, 4H), 2.20 (s, 3H), 2.28 (s, 3H).

Conversion of 7 to 8. Compound **7** (17 mg) was dissolved in 95% ethanol (1 mL), cooled to 0 °C, and treated with $NaBH_4$ (17 mg). After 4 h, glacial AcOH (2 drops) was added to destroy excess reductant. The mixture was concentrated, and brine (2 mL) was added. The mixture was extracted with EtOAc (2 × 4 mL), and the combined organic layers were dried, filtered, and concentrated. The residue was taken into dry pyridine (1 mL) containing DMAP (two crystals) and treated with benzoyl chloride (0.01 μL). After 20 h, the mixture was diluted with EtOAc (5 mL) and washed with 1 M H_2SO_4 (2 × 2 mL), water (4 mL), and then saturated $NaHCO_3$ (4 mL). The organic layer was dried, filtered, and evaporated. The crude product was chromatographed (pipette) using 10:1 PE:Et_2O as eluent to give the benzoate derivative **8** (7 mg). IR υ_{max} (neat): 1760, 1715, 1602, 1584 cm^{-1}. ^{1}H NMR δ: 0.92 (t, 3H, J = 7.0 Hz), 1.00 (t, 3H, J = 7.0 Hz), 1.05 (s, 3H), 1.27 (s, 3H), 1.65 (d, 3H, d = 5.6 Hz), 1.70−2.00 (m, 4H), 2.96 (d, 1H, J = 9.8 Hz), 5.45 (dq, 1H, J = 9.8, 5.6 Hz). ^{13}C NMR, δ: 8.04, 8.83, 19.27, 19.84, 24.10, 24.19, 24.26, 45.54, 54.91, 69.11, 90.16, 128.47, 129.63, 130.02, 130.07, 133.14, 131.70, 149.40, 165.22, 173.98. CI-LRMS (NH_3) m/z (relative intensity): 319.2 (M + 1, 100), 197 (M + 1 − $PhCO_2H$, 52). CI-HRMS calcd for $C_{19}H_{27}O_4$ 319.1909, found 319.1908.

4-[1-(1-Ethyl-3-butenyl)]-3-(methoxycarbonyl)-2-oxooxetane (9a). R_f = 0.40 (4:1 PE:Et_2O). Mixture of diastereomers (1:1). IR υ_{max} (neat): 1835, 1748 cm^{-1}. ^{1}H NMR, δ: 0.98 (t, 3H, J = 8.6 Hz), 1.33−2.33 (m, 5H), 3.81 and 3.82 (s, 3H), 4.21 (d, 1H, J = 4.6 Hz), 4.60−4.70 (m, 1H), 5.00−5.18 (m, 2H), 5.62−5.89 (m, 1H). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.49; H, 7.66.

4-[1-(1-Ethyl-4-pentenyl)]-3-(methoxycarbonyl)-2-oxooxetane (9b). R_f = 0.30 (4:1 PE:Et_2O). Mixture of diastereomers (1:1). IR υ_{max} (neat): 3064, 1834, 1742 cm^{-1}. ^{1}H NMR, δ: 0.96 and 0.97 (t, 3H, J = 7.4 Hz), 1.37−1.85 (m, 5H), 2.00−2.22 (m, 2H), 3.86 (s, 3H), 4.19 (d, 1H, J = 4.6 Hz), 4.69 (dd, 1H, J = 9.2, 4.6 Hz), 4.97−5.13 (m, 2H), 5.68−5.92 (m, 1H). HRMS calcd for $C_{12}H_{18}O_4$ 226.1205, found 226.1201.

4-Ethyl-3-(methoxycarbonyl)-4-(2-propenyl)dihydro-2(3*H*)-furanone (10a). R_f = 0.21 (4:1 PE:Et_2O). Mixture of diastereomers (1:1). IR υ_{max} (neat): 1788, 1732 cm^{-1}. ^{1}H NMR, δ: 0.91 and 0.93 (t, 3H, J = 7.4 Hz), 1.33−1.65 (m, 2H), 2.13 and 2.31 (dd, 2H, J = 13.7, 6.9 Hz), 3.30 and 3.33 (s, 1H), 3.72 and 3.73 (s, 3H), 4.02 and 4.24 (d, 1H, J = 8.8 Hz), 4.10 and 4.20 (d, 1H, J = 8.8 Hz), 5.05−5.25 (m, 2H), 5.56−5.82 (m, 1H). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.25; H, 7.45.

4-(3-Butenyl)-4-ethyl-3-(methoxycarbonyl)dihydro-2(3*H*)-furanone (10b). R_f = 0.17 (4:1 PE:Et_2O). Mixture of diastereomers (1:1). IR υ_{max} (neat): 1784, 1732 cm^{-1}. ^{1}H NMR, δ: 0.89 and 0.93 (t, 3H, J = 7.4 Hz), 1.33−1.70 (m, 4H), 1.95−2.12 (m, 2H), 3.30 and 3.33 (s, 1H), 3.78 (s, 3H), 4.10 (d, 1H, J = 8.6 Hz), 4.22 (d, 1H, J = 8.6 Hz), 4.93−5.12 (m, 2H), 5.62−5.90 (m, 1H). HRMS calcd for $C_{12}H_{18}O_4$ 226.1205, found 226.1207.

5-Ethyl-1-(methoxycarbonyl)-2-oxo-3-oxabicyclo[5.1.0]-octane (11a). R_f = 0.13 (4:1 PE:Et_2O). Compound **11a**, from $Rh_2(pfb)_4$-catalyzed reaction, was obtained as a mixture of diastereomers (**11a-A**:**11a-B** = 3.5:1; ratio was based on the integration of H-6**A** (δ 2.41) and H-6**B** (δ 2.25)). IR υ_{max} (neat): 1740 cm^{-1}. ^{1}H NMR (500 MHz, signals of minor diastereomer in square brackets) δ: 0.55 (dt, J = 16.8, 10 Hz) and 0.88 (t, J = 7.4 Hz) and [0.93, t, J = 7.4 Hz] and [0.92−0.98, m] (3.1H), 1.10−1.13 (m, 1H), 1.28−1.46 (m, 2H) 1.61−1.77 (m) and [1.88−2.01, m, 3H), 2.41 (dt, J = 16.8, 5.0 Hz) and [2.25 (dd, J = 15.1, 3.7 Hz] (1H), 3.75 (s, 3H), [4.05, t, J = 12.0 Hz] and 4.11 (d, J = 12.6 Hz) (1H) and [4.22, dd, J = 12.0, 6.3 Hz] and 4.60 [dd, J = 12.6, 4.3 Hz) (1H). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.19; H, 7.51.

5-Ethyl-1-(methoxycarbonyl)-2-oxo-3-oxabicyclo[6.1.0]-nonane (11b). R_f = 0.09 (4:1 PE:Et_2O). IR υ_{max}: 1732 cm^{-1}. Mixture of diastereomers (**11b-A**:**11b-B** = 1:1; ratio was based on the integration of H-7**A** (δ 2.34) and H-7**B** (δ 2.10−2.18)). ^{1}H NMR (500 MHz, signals of second diastereomer in square brackets) δ: 0.86 (dq, J = 14.7, 12.0 Hz), and [0.92, t, J = 7.2 Hz], 0.96 (t, J = 7.2 Hz) and [0.94−0.99, m] (4.2H), 1.20−1.32 (m, 3.1H), 1.54−1.70 (m, 2.2H), 1.71−1.79 (m, 1.4H), 1.80−1.90 (m, 0.6H), 1.92−1.98 (m, 0.4H), [2.10−2.16, m, 0.5H], 2.40 (dd, 0.5H, J = 14.6, 6.7 Hz), 3.75 (s, 3H), 4.11 (dd, 0.5H, J = 13.0, 1.1 Hz), [4.29, dd, J = 13.1, 4.4 Hz] and 4.31 (dd, J = 12.4, 8.7 Hz) (1H), [4.57, d, 0.5H, J = 12.5 Hz]. Anal Calcd for $C_{12}H_{18}O_4$ (M^+) 226.1205; found: 226.1198.

Decarboxylation of compound 10a To Give γ-Lactone 12. Lactone **10a** (74 mg, 0.35 mmol) was dissolved in a mixture of DMSO (1 mL) and H_2O (0.012 mL) containing powdered NaCl (20 mg, 0.35 mmol). The mixture was heated to 160 °C for 12 h and then cooled to rt. Water (1 mL) was added, the mixture was extracted thoroughly with ether (3 × 10 mL), and the ethereal extracts were washed with brine (10 mL), dried, filtered, and concentrated. The crude product was chromatographed (7:1 and then 4:1 PE:EtOAc) to give **12** (72%). IR υ_{max}(neat): 1778 cm^{-1}. ^{1}H NMR, δ: 0.92 (t, 3H, J = 8.0 Hz), 1.52 (q, 2H, J = 8.0 Hz), 2.21 (br d, 2H, J = 8.0 Hz), 2.28 (d, 1H, J = 18.1 Hz), 2.39 (d, 1H, J = 18.1 Hz), 3.99 (d, 1H, J = 7.4 Hz), 4.09 (d, 1H, J = 7.4 Hz), 5.08−5.20 (m, 2H), 5.60−5.82 (m, 1H). ^{13}C NMR, δ: 8.5, 29.5 (−), 39.2 (−), 40.4 (−), 42.9, 76.4 (−), 119.5 (−), 132.5, 176.9.

3-Ethyl-2-(methoxycarbonyl)-3-(2-propenyl)cyclopentanone (13). Mixture of keto and enol tautomers: IR υ_{max} (neat): 3075, 1756, 1723, 1656, 1614 cm^{-1}. ^{1}H NMR, δ: 0.78 (t, J = 7.7 Hz), 0.91 and 0.93 (t, J = 7.7 Hz)(3H), 1.35−2.50 (m, 8H), 3.05 and 3.09 (s, 0.4H), 3.70, 3.72 and 3.77 (s, 3H), 4.92−5.20 (m, 2H), 5.59−5.89 (m, 1H), 10.95 (s, 0.6H).

Acylation of 13. Compound **13** (22.1 mg, 0.11 mmol) was dissolved in dry CH_2Cl_2 at 0 °C. Pyridine (0.5 mL) was added and stirred for 20 min at 0 °C. Acetyl chloride (12 μL, 0.165 mmol) was added slowly, and the mixture was stirred at 0 °C for 30 min and at rt overnight. The mixture was diluted with CH_2Cl_2, washed with water, saturated aqueous $CuSO_4$, and water, and then dried. The filtered solution was evaporated and the residue chromatographed (20:1 PE:EtOAc) to give **14** (75%). IR υ_{max} (neat): 1775, 1713, 1649 cm^{-1}. ^{1}H NMR, δ: 0.83 (t, 3H, J = 7.7 Hz), 1.40−2.60 (m, 8H), 2.18 (s, 3H), 3.70 (s, 3H), 4.92−5.15 (m, 2H), 5.68−5.90 (m, 1H). ^{13}C NMR, δ: 8.8, 20.8, 28.8 (−), 31.9 (−), 43.9 (−), 51.0, 51.2, 117.3 (−), 122.0, 125.2, 135.2, 159.1, 167.4.

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council, Canada, and the University of Regina for financial support. We also thank Dr. R. Kirk Marat of the Prairie Regional NMR Centre, Manitoba, for the 500 MHz NMR analysis of the cyclopropanated lactones.

Supporting Information Available: Experimental procedure for the preparation of 4-ethyl-6-heptenoic acid and methyl 6-ethyl-3-oxo-8-nonenoate, and 500 MHz NMR data for cyclopropanated lactones **11a**,**b** (28 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO961484D