Macrocyclic Lactones from Dirhodium(II)-Catalyzed Intramolecular Cyclopropanation and Carbon−Hydrogen Insertion

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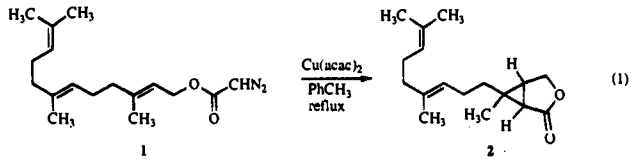
Intramolecular cyclopropanation reactions have been studied since the first report in 1961 of catalytic intramolecular cyclization with an unsaturated diazo ketone.[1] In all examples then and subsequently, intramolecular cyclopropanations formed bicyclo[3.1.0] and bicyclo[4.1.0] rings with great preference over the next higher and lower homologs; extensions beyond bicyclo-[4.1.0]heptan-2-one systems do not occur in meaningful yields.[2-8] Coates and Robinson investigated the catalytic diazo decomposition of *trans,trans*-farnesyl diazoacetate (**1**) and reported formation of the oxabicyclo[3.1.0]hexanone product (**2**, eq 1) as the only cyclopropane-containing product.[9] Numerous other



studies of intramolecular cyclopropanation, where cyclization could have also taken place at a remote carbon−carbon double bond, provided results which clearly indicate that only formation of the bicyclo[3.1.0] or bicyclo[4.1.0] ring systems is viable with catalytic methodologies.[2,6,8]

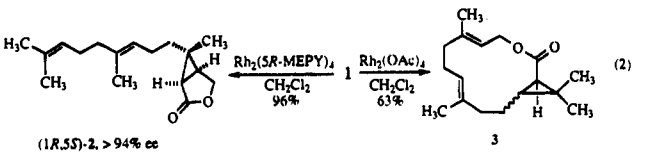
As part of an investigation of the cyclopropanation of *trans,trans*-farnesyl diazoacetate (**1**), catalyzed by chiral dirhodium(II) carboxamides[10] in the development of a synthesis of optically pure presqualene alcohol,[11] dirhodium(II) tetraacetate was used to produce racemic **2** for NMR studies. However, instead of **2**, $Rh_2(OAc)_4$ catalyzed the formation of the 13-membered-ring macrolide cyclopropane-fused lactone **3** in 63% isolated yield (eq 2). This, the first example of macrocycle formation in intramolecular metal carbene transformations, prompted us to undertake this investigation.

Macrocycle **3** was formed as a mixture of two cyclopropane stereoisomers of which the trans form (**3t**) was major. The chromatographically separated isomers (**3t** and **3c**) were identified from NMR experiments (including HETCOR, NOESY, APT), ^1H NMR coupling constants for stereochemical assignments, and mass spectral fragmentations. The macrolide from

Table 1. Influence of Dirhodium(II) Catalyst Ligands on Product Distribution from Diazo Decomposition of *trans,trans*-Farnesyl Diazoacetate (**1**)[a]

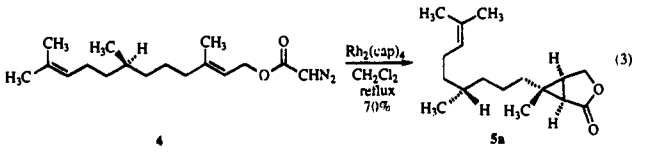
			rel yield, %		
catalyst	temp, °C	isolated yield, %	**2**	**3t**	**3c**
$Rh_2(pfb)_4$	25	56	0	51	49
$Rh_2(pfb)_4$	10	60	0	48	52
$Rh_2(tfa)_4$[b]	25	50	0	77	23
$Rh_2(NHCOCF_3)_4$	25	60	0	75	25
$Rh_2(OAc)_4$	25	63	0	86	14
$Rh_2(oct)_4$[c]	25	50	0	84	16
$Rh_2(cap)_4$[d]	40	79	100	0	0

[a] Reactions were performed in anhydrous CH_2Cl_2 on 1.0 mmol of **1** with 1.0 mol % of catalyst. [b] tfa = trifluoroacetate. [c] oct = octanoate. [d] cap = caprolactamate.



cyclopropanation of the 6,7-double bond of **1** was not observed. The influence on product distribution of dirhodium(II) catalyst ligands,[12] previously established to effectively control chemoselectivity in intramolecular metal carbene transformations[13] as well as regioselectivity and stereoselectivity in intermolecular cyclopropanation reactions,[14] is reported in Table 1. Surprisingly, dirhodium(II) carboxamides, including dirhodium(II) caprolactamate, $Rh_2(cap)_4$,[10] but not dirhodium(II) trifluoroacetamidate,[14,15] and chiral catalysts such as $Rh_2(5R\text{-MEPY})_4$, form **2** exclusively, whereas dirhodium(II) carboxylates abjure **2** in favor of **3**. As has been established previously for intermolecular reactions,[14] increasing electron withdrawal by the catalyst ligand favors **3c** over **3t**. The water insertion product (<10%) and trace amounts of carbene dimers are the only other identified products from these reactions.

In an effort to understand the factors that control macrolide formation, (−)-(7*R*)-6,7-dihydrofarnesol (9:1 *E*/*Z*) was prepared,[16] and its diazoacetate ester (**4**) was subjected to dirhodium(II)-catalyzed diazo decomposition. As expected, use of $Rh_2(cap)_4$ formed **5** (both diastereomers) exclusively (eq 3) and in good yield. Dirhodium(II) acetate and perfluorobutyrate, on



the other hand, did not produce **5** or formed it as a minor product (2% from $Rh_2(OAc)_4$) and, instead, yielded a complex mixture in which macrolide **6** was the major product (23 and 22% yield, respectively), formed as a mixture of *E* and *Z* cyclopropane isomers (54:46 and 58:42, respectively, for trans:cis).

The generality of macrolide formation via intramolecular cyclopropanation was further established from dirhodium(II)-catalyzed reactions of the diazoacetate of (±)-*cis*-nerolidol (**7**).

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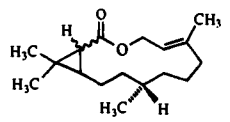

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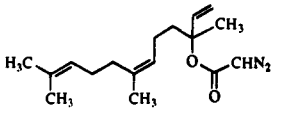

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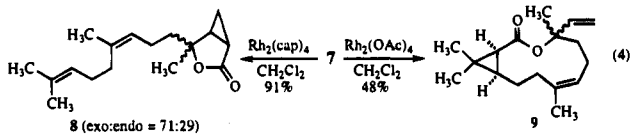
As was now anticipated from results with **1** and **4**, dirhodium(II) caprolactamate catalyzed the formation of products from cyclopropanation of the allylic double bond (**8**), while dirhodium(II) acetate led to the formation (eq 4) of the 11-membered-

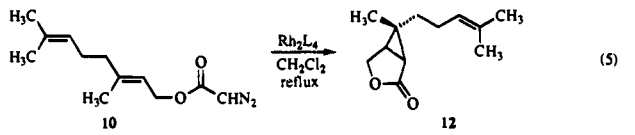


(4)

8 (exo:endo = 71:29)

ring macrolide cyclopropane-fused lactones (**9**). Only the *cis*-cyclopropane stereoisomer of **9** was detected, but the vinyl/methyl stereochemistry was random (50:50). Limited diastereoselection[17] was achieved in the formation of **8**.

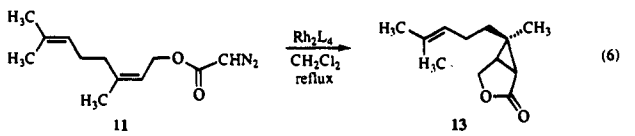
The diazoacetate esters of geraniol (**10**) and nerol (**11**) were also subjected to diazo decomposition. With both, catalysis by $Rh_2(cap)_4$ or $Rh_2(5S\text{-MEPY})_4$ provided the intramolecular cyclopropanation product from addition to the allylic carbon–carbon double bond exclusively in good yield and with high enantiocontrol (eqs 5 and 6). In contrast, use of $Rh_2(OAc)_4$



(5)

10 12

$Rh_2(cap)_4$ 55% yield
$Rh_2(5S\text{-MEPY})_4$ 88% yield (95% ee)

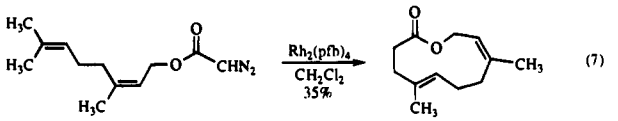


(6)

11 13

$Rh_2(cap)_4$ 48% yield
$Rh_2(5S\text{-MEPY})_4$ 79% yield (93% ee)

under the same conditions, but at room temperature, resulted mainly in the production of carbene dimers, water insertion products, and oligomeric materials that were not characterized; only trace amounts of products from intramolecular metal carbene reactions (<5%) could be detected. However, with $Rh_2(pfb)_4$ the virtual sole product from diazo decomposition of **11** was neither **13** nor the product of intramolecular carbene addition to the C(6),C(7)-position but, rather, a macrolide product from intramolecular carbon–hydrogen insertion into an allylic methyl group at C(8)[18] whose stereochemistry was assigned as depicted in **14** (eq 6, 35% isolated yield) on the basis of NOESY experiments. Although both methyl groups at C(8) are positioned for C–H insertion, the sole formation of **14** demonstrates that the (*E*)-methyl substituent is the exclusive site for insertion, and this process represents the first example of macrolide formation in carbon–hydrogen insertion reactions.



(7)

11 14

Macrolide formation by catalytic intramolecular cyclopropanation and C–H insertion are viable processes with dirhodium(II) carboxylates. The internal, nonallylic, double bond of farnesyl diazoacetate is not essential for cyclopropanation, but the influence of other structural features awaits further investigation. The selectivity achieved for macrolide formation in these catalytic cyclopropanation reactions is in accord with our prior explanation for the mechanism of cyclopropanation[19] wherein electrophilic metal carbenes form π-complexes with the carbon–carbon double bond prior to σ-bond formation.

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Supporting Information Available: Experimental details for the synthesis and diazo decomposition of diazoacetates and product characterizations (13 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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