Enantiocontrol in Macrocycle Formation from Catalytic Metal Carbene Transformations

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The development of catalytic metal carbene transformations for the construction of macrocyclic lactones has dramatically increased their synthetic advantages. This is the first review of this developing methodology.

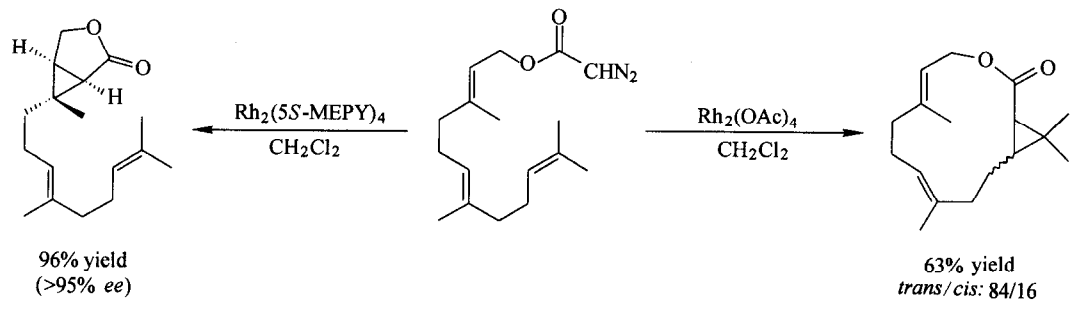
Keywords Macrocylization, dirhodium(II) catalysts, copper(I) catalysts, asymmetric induction, addition reactions, coupling

Background

The synthesis of macrocycles is rich in methodology and important for the construction of numerous biologically significant compounds.[1-4] Although macrocyclic systems can be generated by cleavage of internal bonds in polycyclic systems and by ring expansion,[5] the methods of choice involve entropically disfavored end-to-end cyclization of open, long-chain precursors, generally with the required use of high dilution techniques.[6] Rates for macrocyclization are intermediate between highly favored five- or six-membered ring formation and the intermolecular transformation, and a variety of ingenious processes have been devised to circumvent competition from intermolecular reactions in large ring syntheses.

We have established the generality of a catalytic metal carbene approach to macrocyclic lactones. Our realization of the importance of this methodology began with the report that whereas *trans*, *trans*-farnesyl diazoacetate underwent intramolecular cyclopropanation exclusively at the allylic double bond with catalysis by rhodium(II) carboxamidates, especially $Rh_2(MEPY)_4$ (>95% *ee*), addition took place solely at the terminal double bond with the use of rhodium(II) carboxylates to produce a 13-membered cyclopropane-fused lactone (Scheme 1).[7]

Scheme 1



96% yield
(>95% *ee*)

63% yield
trans/*cis*: 84/16

Mechanism

Those catalysts with reactivities similar to $Rh_2(5S\text{-}MEPY)_4$ (virtually all of the carboxamidates) promoted intramolecular cyclopropanation, whereas those with reactivities of $Rh_2(OAc)_4$, including rhodium(II) trifluoroacetamidate, catalyzed exclusive macrocyclization. These results were consistent with a mechanism for cy-

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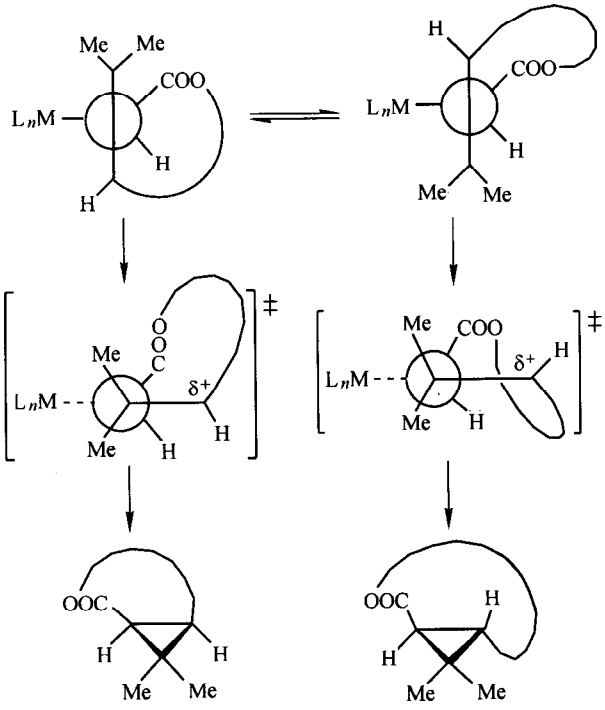
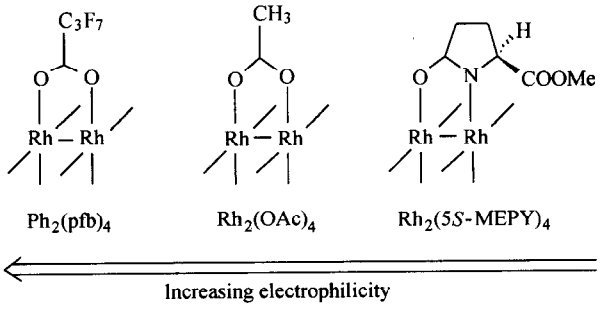
clopropanation that we initially advanced in 1984 and which accounts for the preference of macrocyclization over allylic cyclopropanation.[8] Accordingly, the intermediate metal carbene forms an initial π-complex with the reacting carbon-carbon double bond; rotation of the double bond on the electrophilic carbene center directs the reacting system to the transition state from which bond formation occurs (Scheme 2).

Scheme 2



Such a process can occur with minimum strain in intermolecular addition reactions and when the ring size is sufficiently large to model the intermolecular process. Allylic cyclopropanation, by contrast, presents too constrained a reacting system to undergo initial π-complex formation. In other words, intermolecularand intramolecular macrocyclization addition reactions occur via π-complex formation, whereas allylic intramolecular cyclopropanation proceeds via direct σ-bond formation without the intervention of a π-complex. Consistent with this interpretation, macrocycle formation is a function of the catalyst with the more electrophilic catalysts favoring macrocyclization over intramolecular allylic cyclopropanation while the less electrophilic catalysts favor allylic cyclopropanation (Scheme 3).[9]

Scheme 3

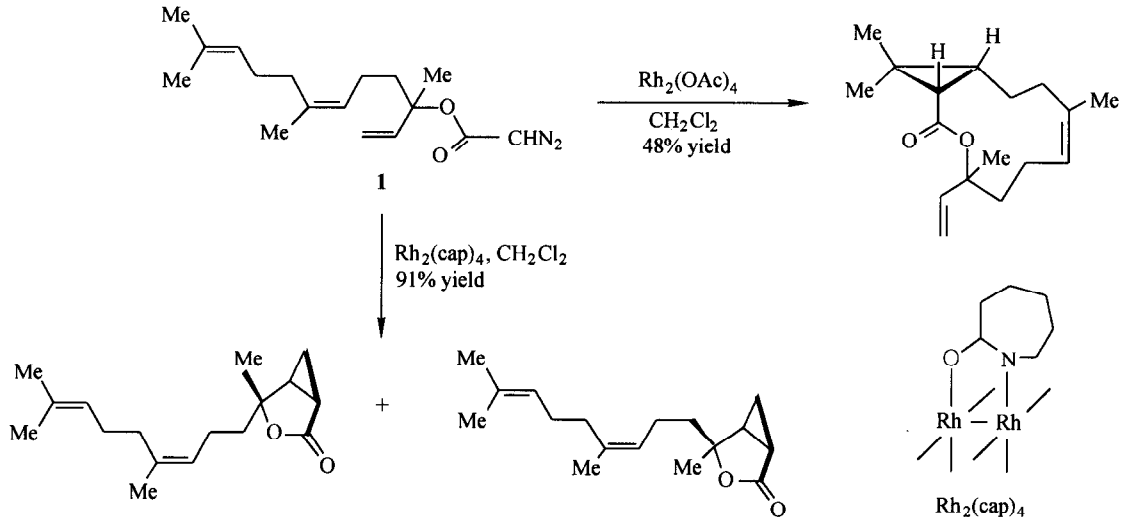


Scope and limitations—cyclopropanation

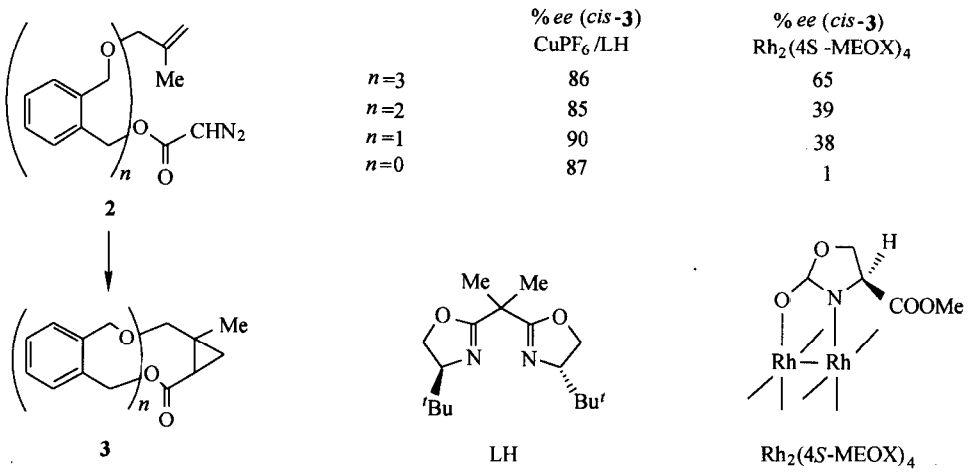
The catalytic intramolecular cyclopropanation by diazoacetates onto a remote carbon-carbon double bond resulting in the formation of 9- to 20-membered ring lactones has been reported.[10] Terpene systems, *cis*-nerolidyl diazoacetate (**1** in Scheme 4) and related structures, malonic ester derivatives, and those with 1,2-benzenedimethanol (**2** in Scheme 5), pentaerythritol, and *cis*-2-buten-1,4-diol in Scheme 6 (**4**) linkers all undergo cyclopropanation onto the most remote carbon-carbon double bond in good yield. Generally, only one cyclopropane diastereoisomer is observed, but increasing ring size allows stereochemistries in macrocyclization reactions that resemble those of their intermolecular cyclopropanation counterparts.[9] Overall, few limits to macrocycle formation are evident, and the methodology appears to have general applicability.[11] The absence of earlier reports of intramolecular macrocyclization[9,12] become understandable when analysis of catalyst reactivity is made.

Enantiocontrol in these reactions has been examined in detail.[13] With the methallyl diazoacetate linked through a 1,2-benzenedimethanol, $CuPF_6$/bis-oxazoline LH caused macrocyclization to occur in high yield and with 90% *ee* (**3**, $n = 1$). With the (*Z*)-2-buten-1,4-diyl diazoacetate derivative **4**, for which both near and remote cyclopropanation are possible, $CuPF_6$/LH preferentially catalyzed formation of the macrocyclic product, whereas $Rh_2(5S\text{-MEPY})_4$ produced the allylic cyclopropanation product exclusively (Scheme 6). The saturated analog of **4** also underwent macrocyclization with $CuPF_6$/LH (91% *ee*). The influence of catalyst on regiocontrol in these reactions is consistent with the electrophilicity of the catalyst, $CuPF_6$/LH being more reactive than $Rh_2(5S\text{-MEPY})_4$.

Scheme 4

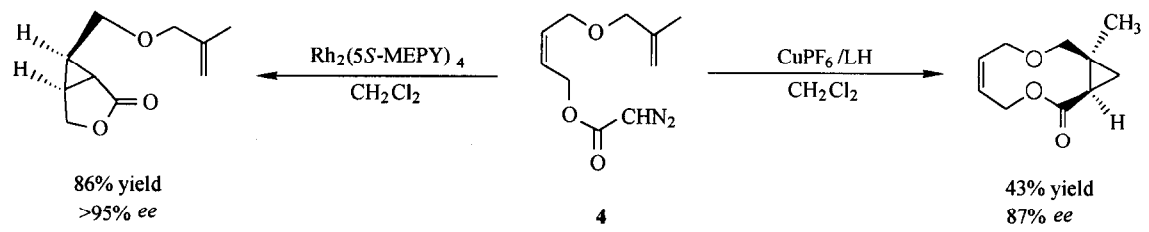


Scheme 5



	% *ee* (*cis*-**3**) $CuPF_6$/LH	% *ee* (*cis*-**3**) Rh_2(4S-MEOX)$_4$
n=3	86	65
n=2	85	39
n=1	90	38
n=0	87	1

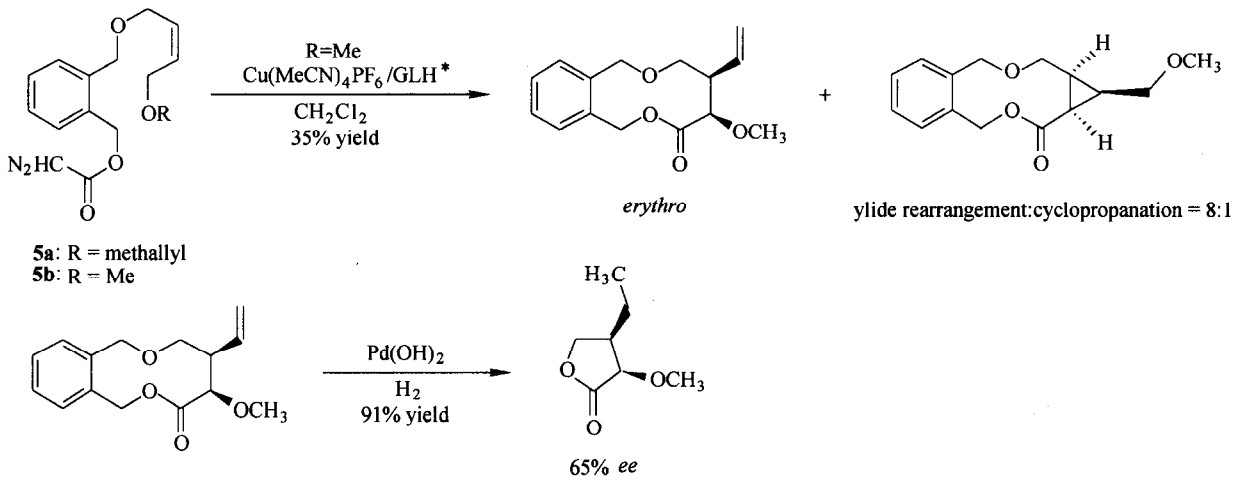
Scheme 6



Ylide Formation and Rearrangement

Extension of this methodology to the formation of larger rings has provided relatively constant enantiocontrol with methallyl systems using $CuPF_6$/LH (Scheme 5). The formation of 15-membered ring product occurs in preference to addition to the *cis*-disubstituted double bond of **5a** that would result in the formation of a 10-membered ring.[13] Interestingly, ylide formation occurs in competition with cyclopropanation, and with methyl (**5b**) or benzyl ethers, moderate enantiocontrol is achieved in the [2, 3]-sigmatropic rearrangement (Scheme 7).[14,15]

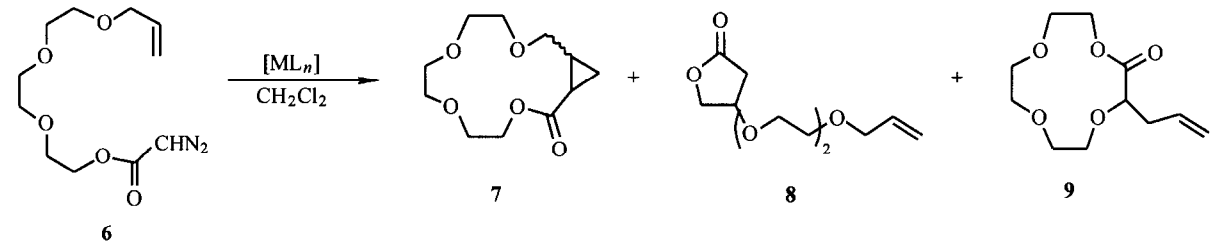
Scheme 7



Even with **5a**, however, the only ylide-derived [2, 3]-sigmatropic rearrangement product results from interaction with the internal, rather than the external double bond.[14] The exclusive formation of the *erythro* (*cis*) isomer demonstrates the exceptional stereocontrol that can be achieved in these transformations.

Similar catalyst dependence on chemoselectivity can be seen in the diazo decomposition of triethylene glycol-linked allyl diazoacetate **6**.[16] $Rh_2(OAc)_4$ catalysis caused formation of macrocyclic cyclopropane **7** (**7**:**8** = 97:3) exclusively while the use of rhodium(II) carboxamidates such as $Rh_2(4R\text{-MEOX})_4$ preferred the C—H insertion product **8** (**7**:**8** = 7:93) (Scheme 8). The *cis*/*trans* ratio of cyclopropane **7** (**7Z**/**7E**) was relatively independent on the catalyst used. Both Cu(I) and Rh(II) catalysts favored the *cis* product **7Z** over **7E** with no more than a 2:1 ratio. In the case of using Cu (I) catalyst, oxonium ylide/[2, 3]-sigmatropic rearrangement occurred to give macrocyclic ester **9** as a minor process (**7**:**9** = 86:14). Good enantioselectivities of macrocyclic cyclopropane **7Z** (88% *ee*) and **7E** (80% *ee*) were obtained by employing Cu(I)(LH)PF_6 catalyst. The use of rhodium(II) carboxamidate catalysts such as $Rh_2(4R\text{-MEOX})_4$ gave moderate *ee*'s of **7** (range from 33% to 59%).

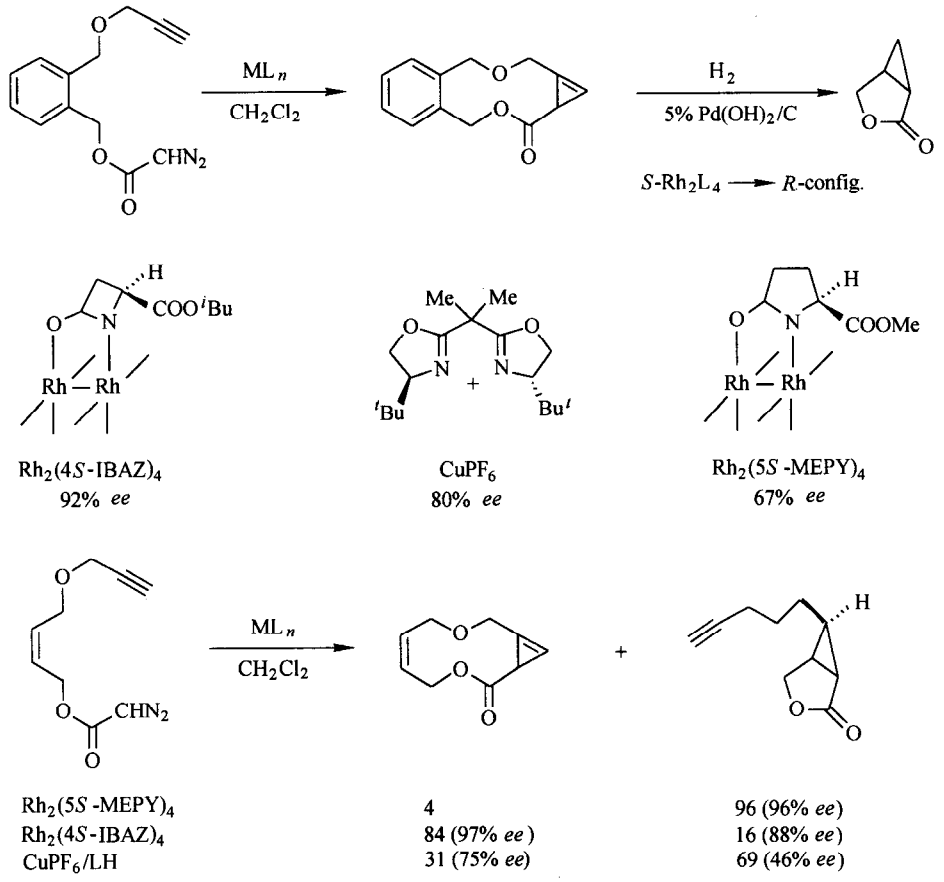
Scheme 8



Scope and Limitations-cyclopropenation

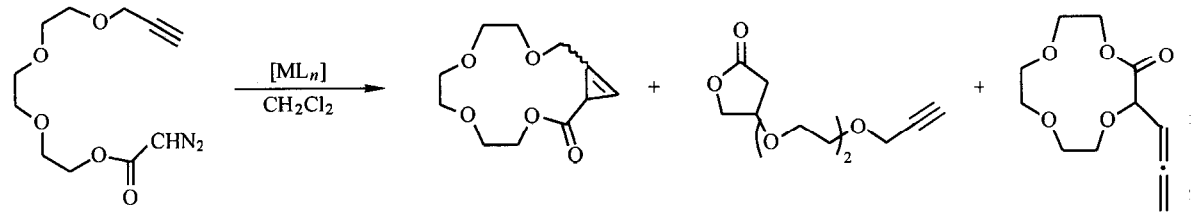
Addition to propargyl ethers gives results that complement the selectivities achieved with intramolecular cyclopropanation reactions.[17,18] Here chiral rhodium(II) carboxamidates, especially $Rh_2(4S\text{-IBAZ})_4$, are even more selective than $CuPF_6$/LH. Several examples are provided that confirm the viability of these reactions (Scheme 9 and 10). Particularly noteworthy is the outcome from reaction of the propargyl system linked to the diazoacetate through a *cis*-2-buten-1,4-diyl linker. Allylic cyclopropanation occurs to the virtual exclusion of macrocyclic cyclopropenation with $Rh_2(5S\text{-MEPY})_4$, whereas this latter transformation is dominant with $Rh_2(4S\text{-IBAZ})_4$.

Scheme 9



In the diazo decomposition of **10**,[16] $Rh_2(4S\text{-}IBAZ)_4$ gave 76% *ee* value of macrocyclic cyclopropene product **11** as a major product (Scheme 10). Interestingly, while exclusive cyclopropanation occurs with $Rh_2(OAc)_4$, ylide formation is a major process in the $Cu(CH_3CN)_4PF_6$-catalyzed diazo decomposition of **10** to give allene product **13** in 46% isolated yield. This process is found to be sensitive to steric effects, however, since none of ylide product **13** was observed by employing Cu (LH) PF_6 catalyst which produced the cyclopropene **11** as the major product in 61% *ee*. Pd-C catalyzed hydrogenation of **11** give only *cis* cyclopropane **7Z** quantitatively without losing enantioselectivity.

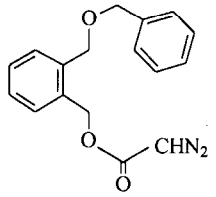
Scheme 10



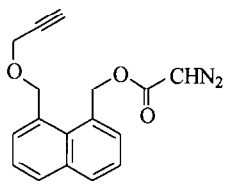
	10	11	12	13
$Rh_2(OAc)_4$		96	4	0
$Cu(CH_3CN)_4PF_6$		25	0	75
$Cu(LH)PF_6$		84 (61% *ee*)	16	0
$Rh_2(4S\text{-}IBAZ)_4$		80 (76% *ee*)	20	0

Aromatic cycloaddition

The addition of a metal carbene to an aromatic ring is also a viable transformation for macrocycle formation.[19,20] Exclusive addition to the 3,4-position of the 4-methoxybenzyl derivative of **14** occurs in reactions catalyzed by $Rh_2(OAc)_4$, but the more reactive $Rh_2(pfb)_4$ also produces the product from addition to the 1,2-position as a minor constituent of the reaction mixture (13:87). With **15**, which upon diazo decomposition can undergo either addition to the carbon-carbon triple bond or addition to the aromatic ring, aromatic cycloaddition occurs exclusively when $Rh_2(MEOX)_4$ is employed (66% yield, 73% *ee*), although other dirhodium(II) catalysts, including $Rh_2(OAc)_4$, favor macrocycle formation.



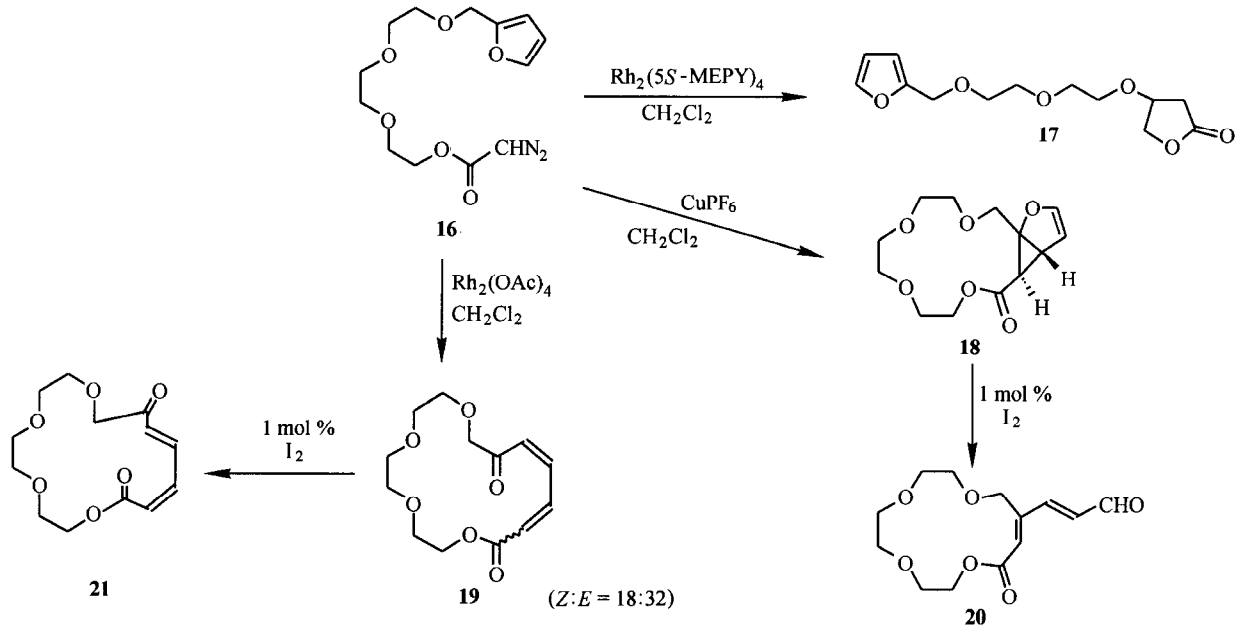
14



15

The extent to which this macrocyclization process can be used for the preparation of large-ring esters can be seen in results from diazo decomposition of the diazoacetate **16** derived from triethylene glycol (Scheme 11).[21] Catalysis by $Rh_2(5S\text{-MEPY})_4$ gave only the product from C-H insertion (**17**) in high yield even though the use of the model carboxamidate $Rh_2(cap)_4$, resulted in a mixture of products in which both **17** (major) and **19** (minor) were evident. In contrast, use of $Cu(MeCN)_4PF_6$ gave mainly **18** and dirhodium(II) octanoate, $Rh_2(OAc)_4$ and $Rh_2(OAc)_4$ gave mainly ring-opened products **19**. The product from *anti* addition, *E*-**19**, was favored over the product from *syn* addition, *Z*-**19**, in this case. Furthermore, **18** was converted to **20** by treatment with 1 mol % I_2 in chloroform, and **19** was isomerized to **21** quantitatively. Other transformations are being examined in what appears to be a general outcome in metal carbene reactions. The surprising feature of these macrocyclization reactions, in addition to their design, is the absence of a requirement for high dilution. These reactions are performed successfully under the same conditions as have been used for allylic cyclopropanation reactions.

Scheme 11

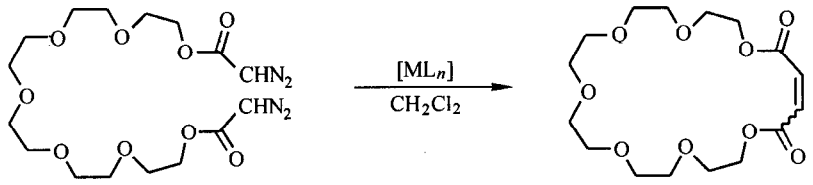


Coupling

Intramolecular coupling of bisdiazo compounds is another effective method for macrocycle formation.[22] Thus bisdiazoacetate **22** underwent coupling catalyzed by Cu(I) or Rh(II) to give the 23-membered ring crown

ether **23** in good yield (Scheme 12). The *cis/trans* selectivity was dependent on the catalyst used. $CuPF_4$ gave *trans* product **23Z** exclusively while $Rh_2(5R\text{-MEPY})_4$ preferred to form *cis* isomer. No high dilution technique was required and none of intermolecular coupling product was observed in this process.

Scheme 12



22 **23**

	yield (%)	**23Z/23E**
$Cu(CH_3CN)_4PF_6$	73	18:82
$Rh_2(5R\text{-MEPY})_4$	75	76:24

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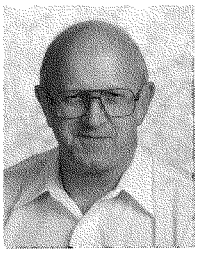

Michael P. Doyle was born in Minneapolis, MN. He received his B.S. degree from the College of St. Thomas in St. Paul, MN, and, working under the direction of Walter S. Trahanovsky, obtained his Ph.D. degree from Iowa State University. Following a postdoctoral engagement with Jan Rocek at the University of Illinois at Chicago Circle, he joined the faculty at Hope College in 1968. In 1984, he moved to Trinity University in San Antonio, TX, as Dr. D. R. Semmes Distinguished Professor of Chemistry, and in 1997 he moved to Tucson, AZ, where he is Professor of Chemistry at the University of Arizona and Vice President of Research Corp. Professor Doyle has been the recipient of a Camille and Henry Dreyfus Teacher-Scholar Award (1973), a Chemical Manufacturers Association Catalyst Award (1982), the American Chemical Society Award for Research at Undergraduate Institutions (1988), Doctor Honoris Causa from the Russian Academy of Sciences (1994), Alexander von Humboldt Senior Scientist Award (1995), and the James Flack Norris Award for Excellence in Undergraduate Education (1995), and he is the co-author of more than 230 publications. His research interests include asymmetric catalysis and its applications, the design and development of dirhodium(II) compounds, metal carbene chemistry, and new methods for the synthesis of macrocyclic compounds.

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