Selectivity in Reactions of Allyl Diazoacetates as a Function of Catalyst and Ring Size from γ-Lactones to Macrocyclic Lactones

Michael P. Doyle* and Wenhao Hu

Department of Chemistry, University of Arizona, Tucson, Arizona 85721

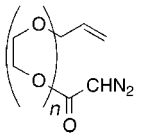
mdoyle@u.arizona.edu

Received July 25, 2000

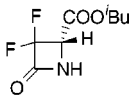
Catalytic reactions of diazoacetates tethered through zero, one, two, and three ethylene glycol units to an allyl group have been investigated for chemoselectivity, diastereoselectivity, and enantioselectivity. Results from cyclopropanation, carbon−hydrogen insertion, and oxonium ylide generation are compared from reactions of achiral and chiral catalysts of copper(I) and dirhodium(II) carboxylates and carboxamidates. Relative to results from intermolecular reactions of ethyl diazoacetate with allyl ethyl ether, intermolecular reactions show a diversity of selectivities including preference for the opposite configurational arrangement from the one preferred in corresponding intermolecular cyclopropanation reactions. Enantioselectivities for cyclopropanation are dependent on the catalyst ligands in a manner that reflects divergent trajectories of the carbon−carbon double bond to the reacting carbene center. Enantioselectivity increases as a function of ring size with chiral copper catalysts, but the reverse occurs with chiral dirhodium(II) carboxamidates. Mechanistic implications, including those related to the conformation of the reacting metal carbene, offer a new dimension to understanding of enantioselectivity in catalytic asymmetric cyclopropanation reactions.

In recent years, we have reported the unprecedented effectiveness of intramolecular cyclopropanation reactions of diazo esters as an effective entry into macrocyclic lactones.[1,2] These reactions appear to have broad generality and to occur with moderate to high levels of enantiocontrol when selected chiral catalysts are employed.[3] What is missing is an understanding of the influence of ring size on selectivity as a function of catalyst.[4,5] Can one generalize the influence of specific catalysts or see trends? For example, is there a trend toward selectivities obtained in intermolecular reactions from intramolecular cyclopropanation as ring size is increased, and can mechanistic information be obtained from these selectivities?

We have investigated catalytic reactions of diazoacetates tethered through zero, one, two, and three ethylene glycol units to an allyl group (**1**), and we compare these results with those from intermolecular reactions of ethyl diazoacetate with allyl ethyl ether. Both copper(I) and dirhodium(II) catalysts have been employed, including the highly reactive dirhodium(II) carboxamidate derived from isobutyl 3,3-difluoro-2-oxaazetidine-(4*R*)-carboxylate (**2**). We now report the chemoselectivity, diastereoselectivity, and enantioselectivity of these reactions and describe the generalities that can be drawn from the data.



1 (*n* = 0,1,2,3)



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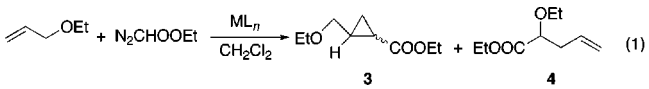
Results

That dirhodium(II) acetate-catalyzed reactions of ethyl diazoacetate with allyl ethyl ether yields cyclopropane products (**3**) predominantly together with a low yield of the product from oxonium ylide generation followed by [2,3]-sigmatropic rearrangement (**4**) has been previously established.[6] Data from this same reaction (eq 1) catalyzed by chiral copper(I) and dirhodium(II) catalysts are reported in Table 1. Note that cyclopropanation is



(1)

3 **4**

exclusive or virtually so with all of the dirhodium(II) catalysts (**5**−**9**), but ylide formation is a competitive process with copper(I) catalysts. The trans-disubstituted cyclopropane product is favored with Cu(I) catalysts and with dirhodium(II) carboxylates, but not carboxamidates. The highest % ee value obtained for *trans*-**3** came from $CuPF_6$/**10**, while **7** and **8** provided the highest % ee values for *cis*-**3**. This latter observation is consistent with results previously obtained with styrene and other monosubsti-

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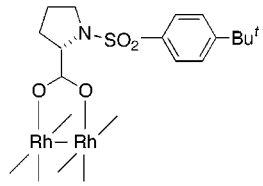
10.1021/jo005589z CCC: $19.00
Published on Web 11/29/2000

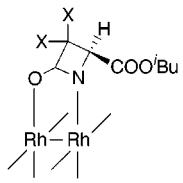
Table 1. Chemoselectivity, Diastereoselectivity, and Enantioselectivity from Catalytic Reacations of Ethyl Diazoacetate with Allyl Ethyl Ether[a]

catalyst	yield,[b] %	**3**:**4**[c]	*trans*-**3**/ *cis*-**3**[c]	% ee[d] *trans*-**3**	*cis*-**3**	4
$Rh_2(OAc)_4$	74	95:5	62:38			
$Cu(MeCN)_4PF_6$	87	62:38	70:30			
$CuPF_6$/**10**	61	73:27	81:19	75	43	60
Rh_2(*S*-TBPRO)$_4$ (**5**)	50	100:0	84:16	4	5	
Rh_2(4*R*-dFIBAZ)$_4$ (*ent*-**6**)	34	97:3	52:48	38	19	30
Rh_2(4*S*-IBAZ)$_4$ (**7**)	63	100:0	43:57	48	67	
Rh_2(5*S*-MEPY)$_4$ (**8**)	64	100:0	56:44	37	70	
Rh_2(4*R*-MEOX)$_4$ (**9**)	53	100:0	58:42	7	48	

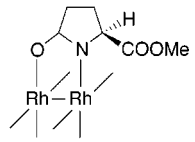
[a] Reactions performed by addition of EDA in CH_2Cl_2 to a refluxing CH_2Cl_2 solution containing allyl ethyl ether (10 equiv) and catalyst (1.0 mol %). [b] Isolated yield of **3** + **4** after chromatographic separation. [c] Determined by GC on an SPB-5 column. [d] Determined by GC on a Chiraldex B-DM column.



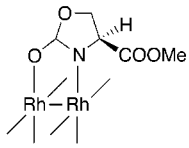
Rh_2(*S*-TBPRO)$_4$
5[7]



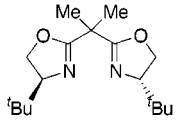
X = F: Rh_2(4*S*-dFIBAZ)$_4$ (**6**)
X = H: Rh_2(4*S*-IBAZ)$_4$ (**7**)[8]



Rh_2(5*S*-MEPY)$_4$
8[9]



Rh_2(4*S*-MEOX)$_4$
9[10]



10[11]

tuted alkenes.[12] The predominant enantiomer for either *trans*-**3** or *cis*-**3**, as well as for ylide product **4**, formed via catalysis with Cu(I)/**10**, **5**, or *ent*-**6** is opposite of that formed via catalysis with **7**−**9**.

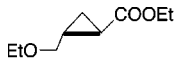
The absolute configurations of products formed by asymmetric catalytic intermolecular cyclopropanation have been established in many cases,[4,5] although not from reactions with allyl ethyl ether. With styrene and ethyl diazoacetate, for example, the predominant enantiomers formed with Cu(I)/**10** as the catalyst are (1*R*,2*R*) for the trans isomer and (1*R*,2*S*) for the cis isomer.[4] The opposite preference is obtained with Rh_2(5*S*-MEPY)$_4$,[4,12] and *S*-configured dirhodium(II) carboxamidates in the sense of **7**−**9** direct product formation to those having the same absolute configuration. On the basis of these considerations and the similarity of **3** to products of known

Table 2. Enantioselectivity from Catalytic Reactions of 11[a]

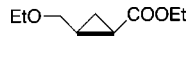
catalyst	**11** yield,[b] %	**11** % ee[c]
$CuPF_6$/**10**	61	20 (1*R*,5*S*)
Rh_2(4*S*-IBAZ)$_4$ (**7**)	92	80 (1*R*,5*S*)
Rh_2(5*S*-MEPY)$_4$ (**8**)	75	95 (1*R*,5*S*)
Rh_2(4*S*-MEOX)$_4$ (**9**)	95	94 (1*R*,5*S*)

[a] Reactions performed by addition of **11** in CH_2Cl_2 to a refluxing CH_2Cl_2 solution of catalyst (<1.0 mol %). [b] Isolated yield of **11** after chromatographic separation from the catalyst and carbene dimers. [c] Absolute configuration given in parentheses.

absolute configuration, we suggest that the dominant enantiomer of *trans*-**3** formed with Cu(I)/**10**, **5**, and *ent*-**6** has the (1*R*,2*R*)-configuration, while catalysts **7**−**9** produce *trans*-**3** having the (1*S*,2*S*)-configuration predominantly. Similarly, for the cis isomer (1*R*,2*S*)-**3** is favored with Cu(I)/**10**, **5**, and *ent*-**6**, but (1*S*,2*R*)-**3** is favored with **7**−**9**.

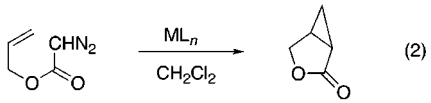


(1*R*,2*R*)-**3**



(1*R*,2*S*)-**3**

Contrast these results with those from catalytic reactions of allyl diazoacetate (eq 2)[13−15] from which **12** is formed as the sole product with enantiocontrol that is exceptionally high (95% ee) with Rh_2(MEPY)$_4$ catalysts and disappointingly low with $CuPF_6$/**10** (Table 2).[14] The



11 **12** (2)

absolute configuration of **12** formed in each of these catalytic reactions has been established,[13] and in this case all of the catalysts in Table 2 give rise to (1*R*,5*S*)-**12**. The effects of alkene substituents on enantiocontrol have been determined, and they have formed the bases for current mechanistic understanding of this intramolecular addition reaction.[13] Note that the absolute configuration of **12** formed by all of dirhodium(II) carboxamidates listed in Table 2 is opposite to that found in the intermolecular cyclopropanation reaction (eq 1).

Consider now the case with the allyl group separated from diazoacetate by one ethylene glycol unit. In catalytic reactions cyclopropanation would form the disfavored eight-membered ring; however, there are few examples of medium ring formation in all of the catalytic cyclopropanation literature.[4,15−18] A favorable competing transformation is intramolecular carbon−hydrogen insertion into the ether-oxygen-activated position (five-membered ring formation),[4,19,20] as also might be intramolecular

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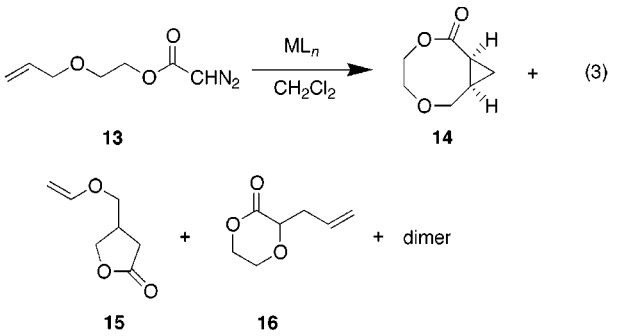
Table 3. Chemoselectivity and Enantioselectivity from Catalytic Reactions of 13[a]

catalyst	yield,[b] %	**14**−**16**/ dimer[c]	**14**:**15**:**16**[c]	% ee **14**[d]	% ee **15**[e]	% ee **16**[d]
$Rh_2(OAc)_4$	93	91:9	77:17:6			
$Cu(MeCN)_4PF_6$	87	34:66	26:0:74			
$CuPF_6$/**10**	61	12:88	14:30:56	67	22	6
$CuPF_6$/**10**[e]	61	74:26	7:12:81	71	27	8
Rh_2(*S*-TBPRO)$_4$ (**5**)	50	96:4	88:5:7	28	19	18
Rh_2(4*R*-dFIBAZ)$_4$ (*ent*-**6**)	34	42:58	29:32:39	19	62	88
Rh_2(4*S*-IBAZ)$_4$ (**7**)	63	81:19	5:95:0	49	91	
Rh_2(5*S*-MEPY)$_4$ (**8**)	64	98:2	0:100:0		91	
Rh_2(4*R*-MEOX)$_4$ (**9**)	78	99:1	0:98:2		96	94

[a] Reactions performed by addition of **13** in CH_2Cl_2 to a refluxing CH_2Cl_2 solution of catalyst (1.0 mol %). [b] Isolated yield of **14**−**16** + dimer after chromatography. [c] Determined by GC on a SPB-5 column. [d] Determined by GC on a Chiraldex B-DM column. [e] Determined by GC on a Chiraldex G-−TA column. [e] Catalyst was diluted 20X-greater than in other reported runs.

oxonium ylide formation followed by [2,3]-sigmatropic rearrangement (six-membered ring formation).[21] In fact, the products from each of these intramolecular transformations—cyclopropanation, C−H insertion, and oxonium ylide formation/[2,3]-sigmatropic rearrangement—are observed (eq 3). Results from this investigation as a



function of catalyst are reported in Table 3. The predominant enantiomer of **14** formed with $CuPF_6$/**10** and with **5** and *ent*-**6** is opposite to that formed with **7**−**9**. By analogy with the preferred configuration of **12** and through rotational (same sign) and chromatographic (same order of elution) correlations, the dominant enantiomer of **14** formed by catalysis with **7** is assigned (1*R*,8*S*); that from catalysis with $CuPF_6$/**10**, **5**, and *ent*-**6** is assigned (1*S*,8*R*). The dimer that is reported in eq 1 and Table 3 is that of "carbene dimer" formation, an intermolecular reaction product that serves as a kinetic monitor of the ease or difficulty of intramolecular reactions. Since reaction conditions for each catalyzed diazo decomposition were identical, the extent of dimer formation is a direct measure of the sum of the relative rates for intramolecular reactions (Scheme 1). Accordingly, use of the more reactive catalysts[22]—those of copper(I) and of *ent*-**6**—resulted in the formation of carbene dimers as the predominant reaction process. Note that, consistent with Scheme 1, a 20-fold dilution of the catalyst solution with $CuPF_6$/**10** caused a more than 3-fold decrease in the amount of carbene dimer.

Because of the strain imparted into the ring upon its formation, **14** was a major product only with the use of

Scheme 1

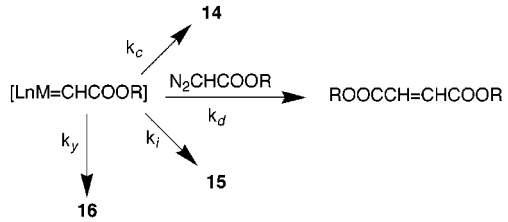


Table 4. Chemoselectivity, Diastereoselectivity, and Enantioselectivity from Catalytic Reactions of 17[a]

catalyst	yield,[b] %	**18**:**19**[c]	*Z*-**18**:*E*-**18**[c]	% ee[d] *Z*-**18**	% ee[d] *E*-**18**	% ee[d] **19**
$Rh_2(OAc)_4$	83	96:4	87:13			
$Cu(MeCN)_4PF_6$	64	100:0	91:9			
$CuPF_6$/**10**	58	100:0	86:14	79	85	
Rh_2(*S*-TBPRO)$_4$ (**5**)	80	98:2	87:13	11	12	14
Rh_2(4*R*-dFIBAZ)$_4$ (*ent*-**6**)	67	85:15	84:16	33	67	75
Rh_2(4*S*-IBAZ)$_4$ (**7**)	69	42:58	88:12	56	64	90
Rh_2(5*S*-MEPY)$_4$ (**8**)	77	5:95	88:12	53	65	92
Rh_2(4*R*-MEOX)$_4$ (**9**)	73	1:99	88:12	48	67	92

[a] Reactions performed by addition of **17** in CH_2Cl_2 to a refluxing CH_2Cl_2 solution of catalyst (1.0 mol %). [b] Isolated yield of **18** + **19** after chromatography. [c] Determined by GC on a SPB-5 column. [d] Determined by GC on a Chiraldex B-TA column.

dirhodium(II) carboxylates. Dirhodium(II) carboxamidates favored C−H insertion, and **15** was formed with the high enantiocontrol anticipated from earlier studies.[23] The major enantiomer of C−H insertion product **15** formed with catalysts **7**-**9** is assigned (4*S*)—the same as that reported previously from reactions of a wide variety of diazo substrates.[4,5,23,24] In contrast, with copper(I) catalysts oxonium ylide formation leading to **16** was dominant. The high enantiocontrol for **16** that was observed with dirhodium(II) carboxamidate catalysts *ent*-**6** and **9** reflected results from previously reported systems,[25] and signaled once again the importance of metal-associated ylides as reaction intermediates,[25−27] as well as the role of ligands on the metal for a high level of asymmetric induction in the product-forming step.

The outcome of these intramolecular reactions changes once again when the allyl group is separated from diazoacetate by two ethylene glycol units. In this case intramolecular cyclopropanation would form an eleven-membered ring (**18**), whereas oxonium ylide formation that could lead to product via [2,3]-sigmatropic rearrangement would require the intervention of a nine-membered ring (**20**). The results from diazo decomposition of **17** (eq 4) reflect these considerations (Table 4). With this system, copper(I) catalysts and dirhodium(II) carboxylates form macrocyclic lactone **18** almost exclusively whereas dirhodium(II) carboxamidates Rh_2(5*R*-MEPY)$_4$ and Rh_2(4*S*-MEOX)$_4$ give the product from intramolecular C−H insertion (**19**) almost exclusively.

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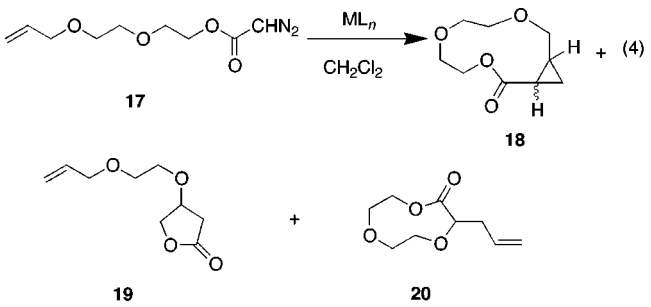
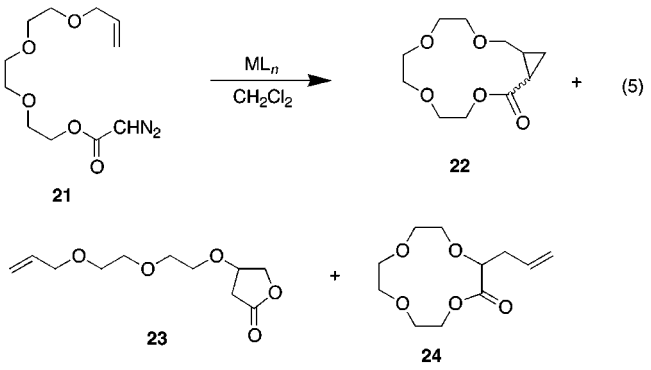


The azetidinone-ligated dirhodium(II) catalysts, whose reactivities fall between those of the carboxylates and carboxamidates **8** and **9** yield both **18** and **19**. Here again, the dominant enantiomer of *Z*-**18** formed by catalysis with dirhodium(II) carboxamidates **7**−**9** is assigned the (1*R*,11*S*) configuration; catalysis by $CuPF_6$/**10**, **5**, and *ent*-**6** gave the enantiomer of opposite configuration predominantly. Both the cis and trans fused rings of **18** were observed in this case, but their ratio was invariant with the catalyst. Although absolute configuration is not assigned for *E*-**18**, we can report that the dominant enantiomer formed by catalysis with **7**−**9** is opposite to that formed by catalysis with $CuPF_6$/**10**, **5**, and *ent*-**6**. Enantioselectivities for intramolecular cyclopropanation by the dirhodium(II) carboxamidates varied from catalyst to catalyst by only a small degree, and they were moderately less than those from $CuPF_6$/**10**. The predominant enantiomer in $CuPF_6$/**10**-catalyzed reactions was opposite to that found from reactions catalyzed by chiral dirhodium(II) carboxamidates. Ylide-derived **20** was not detected except perhaps as a minor constituent in $CuPF_6$-catalyzed reactions.

Finally, with three interlinked ethylene glycol spacers between allyl and diazoacetate, the three intramolecular processes that we have been reporting—cyclopropanation, C−H insertion, and oxonium ylide generation/[2,3]-sigmatropic rearrangement—were all observed (eq 5). The



results from diazo decomposition of **21** with copper(I) and dirhodium(II) catalysts are reported in Table 5. Here again, macrocyclic cyclopropanation dominates with $Rh_2(OAc)_4$ and with copper catalysts, and intramolecular C−H insertion leading to γ-lactone **23** is preferred with the less reactive dirhodium(II) carboxamidates, Rh_2(5*S*-MEPY)$_4$ and Rh_2(4*R*-MEOX)$_4$. Ylide formation is a minor process with copper catalysts but is not observed with dirhodium(II) catalysts. Enantioselectivity and enantiomer preferences in cyclopropanation with **21** match those found with **17** and with **14**, and preference for the (1*R*,n*S*)- or (1*S*,n*R*)-configuration of these cyclopropanation products is opposite to that found in the intermolecular reaction (eq 1) as a function of catalyst. Enantiomers of C−H insertion product **23** could not be separated, but selectivity could be assumed to be approximately that found for **19** (Table 4).

Table 5. Chemoselectivity, Diastereoselectivity, and Enantioselectivity from Catalytic Reactions of 21[a]

catalyst	yield,[b] %	**22**:**23**:**24**[c]	*Z*-**22**: *E*-**22**[c]	% ee[d] *Z*-**22**	*E*-**22**	**24**
$Rh_2(OAc)_4$	65	97:3:0	64:36			
$Cu(MeCN)_4PF_6$	65	86:0:14	56:44			
$Cu(PhCOCHCOCH_3)_2$	82	90:0:10	47:53			
$CuPF_6$/**10**	73	83:13:4	40:60	88	80	27
Rh_2(4*R*-dFIBAZ)$_4$ (*ent*-**6**)	56	83:13:0	65:35	37	26	
Rh_2(4*S*-IBAZ)$_4$ (**7**)	70	53:47:0	65:35	59	44	
Rh_2(5*S*-MEPY)$_4$ (**8**)	61	13:87:0	63:37	49	44	
Rh_2(4*R*-MEOX)$_4$ (**9**)	67	7:93:0	64:36	47	33	

[a] Reactions performed by addition of **21** in CH_2Cl_2 to a refluxing CH_2Cl_2 solution of catalyst (1.0 mol %). [b] Isolated yield of **22**−**24** after chromatography. [c] Determined by GC on a SPB-5 column. [d] Determined by GC on a Chiraldex B-PH column.

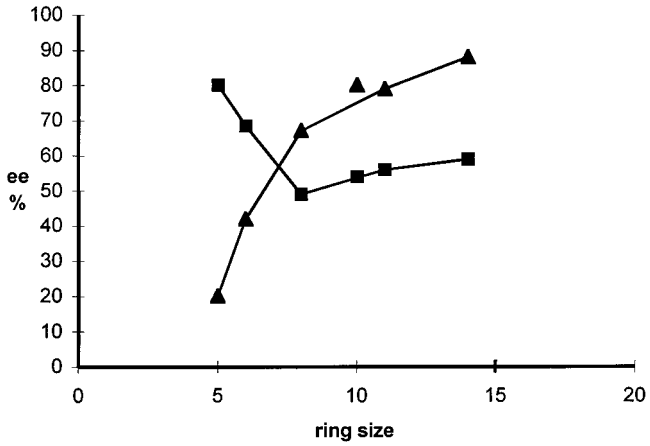


Figure 1. Ring size versus % ee for reactions of **11**, **27**, **13**, **28**, **17**, and **21** with catalysts $CuPF_6$/**10** (▲) and Rh_2(4*S*-IBAZ)$_4$ (**7**) (■).

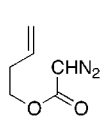
Discussion

A plot of % ee versus ring size (Figure 1) for cyclopropanation (*Z*-only) reveals a pattern that reflects the geometrical differences between Cu(I)/**10** (trans array, **25**) and dirhodium(II) carboxamates (cis array, **26**) and their influences on olefin trajectories to the carbene center.[3]

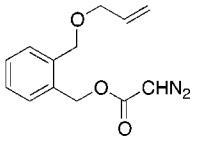
Cu(I)/**10**, **25**
trans array
(A = *t*-Bu)
R-configuration

Rh_2L_4, **26**
cis array
(E = COOR)
S-configuration

Notice that as ring size increases, % ee for the *Z*-isomer decreases with chiral dirhodium(II) catalysts **7**−**9**, whereas % ee increases significantly through the formation of **14** and **18** to **22** for chiral $CuPF_6$/**10**. Confirmation of these trends can be seen in results from intramolecular cyclopropanation of homoallylic diazoacetate **27**[13] and of allylic diazoacetate **28**,[3] the results for which are also found in Figure 1.



27



28

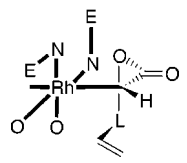
Furthermore, in a series of benzenedimethanol-linked methallyl diazoacetates, % ee for the *Z*-isomer was found to increase with increasing ring size for chiral dirhodium(II) carboxamidates but remain virtually unchanged with chiral $CuPF_6$/**10**. These quite different results reflect divergent trajectories of the carbon−carbon double bond toward the carbene center for copper(I) and rhodium(II) catalysts.

In the formation of the cyclopropane *E*-isomers, % ee values for *E*-**18** and *E*-**22** appear to be moving toward limiting values from the intermolecular cyclopropanation product *trans*-**3**. The same cannot be said for *Z*-isomers from **18** and **22** which do not appear to be moving toward limiting values of *cis*-**3**. However, diastereoselectivities from intramolecular cyclopropanation reactions do approach those from intermolecular cyclopropanation as ring size is increased.

As seen by the results from intermolecular cyclopropanation of allyl ethyl ether (Table 1), copper catalysts and rhodium(II) carboxylates show a marked preference for the *trans*-cyclopropane isomer whereas rhodium(II) carboxamidates are more amenable to the formation of the thermodynamically less stable *cis*-cyclopropane isomer. However, where ring strain is not appreciable, the *cis*-cyclopropane isomer is preferred in intramolecular cyclopropanation for all catalysts to a ring size of fourteen. There is a dramatic difference in % ee values between trans (*E*) and cis (*Z*) cyclopropane isomers formed by intermolecular cyclopropanation (Table 1) but not by intramolecular cyclopropanation (Tables 4 and 5).

When the *cis*-cyclopropane isomer is formed in intramolecular cyclopropanation reactions, enantiocontrol can be represented as being dependent upon trajectories **29** and **30** (Scheme 2, L = linker), previously described with reference to the limiting conformations available for product formation,[3,14] as well as the mirror image representations of **29** and **30**. Trajectories **29** and **30** are the configurations preferred for the *S*-configured dirhodium(II) carboxamidates.[9] Results obtained for intramolecular cyclopropanation with dirhodium(II) carboxamidates in this study, and in prior investigations of the influence of alkene substituents on enantiocontrol,[13,14] are consistent with reactions occurring through trajectory **29** and its mirror image, and influences from **30** are consistent with the dominant stereochemistry for Cu(I)/**10**-catalyzed reactions.

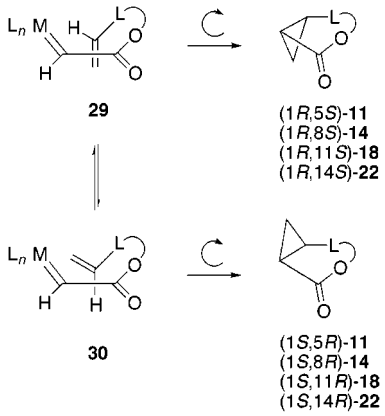
The rotational preference of the alkene about the carbene center is clockwise in **29** and **30**, an example for which is depicted in **29A** for the reactions that occur on an *S*-configured dirhodium(II) carboxamidate (*E* = ester).



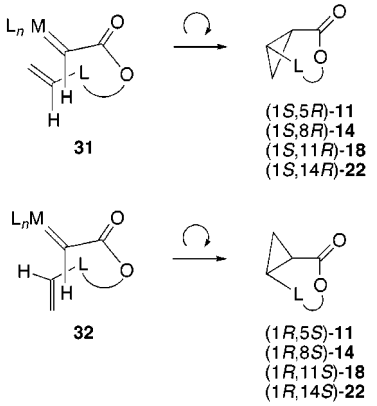
29A

The conformation identified here was previously indicated as a preferred energy minimum through computational analyses.[9] In this depiction, looking down the carbon−rhodium bond, the direction of the ligand carboxylate esters (*E*), is counterclockwise, but the motion of the alkene to the carbene center is clockwise.

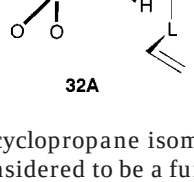
Scheme 2



Scheme 3



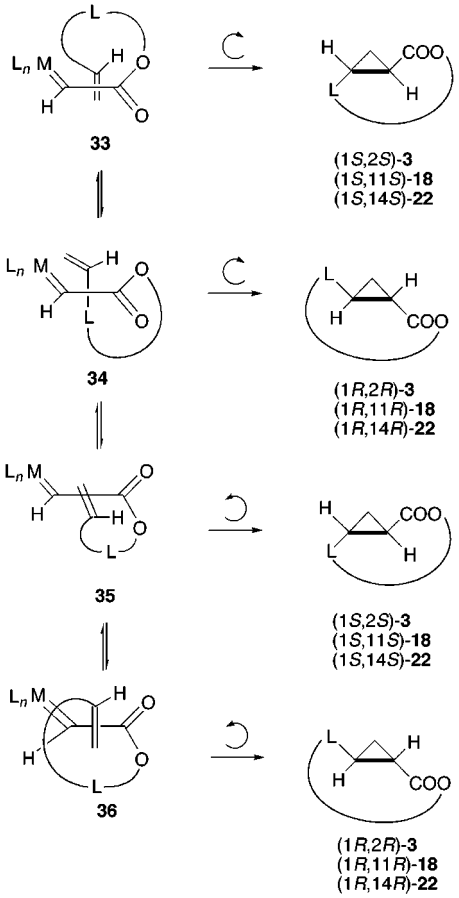
These trajectories are based on the alignment of the carbene carbonyl oxygen anti to the transition metal. Syn alignments are also possible and, as depicted in Scheme 3, can be used with the same mode of clockwise or counterclockwise rotation to designate the observed products. Application of these conformations actually leads to the prediction of preference for the correct enantiomer in intramolecular cyclopropanation reactions, but because the alkene is placed even farther from the influence of the metal (**32A**) than in **29A**, and as a result of the preference for the carbonyl syn to the metal through computational analysis,[9] we prefer to use **29** and **30**.



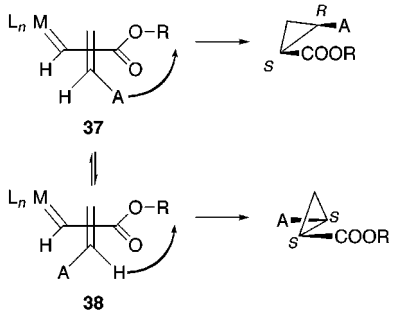
32A

When the *trans*-cyclopropane isomer is formed, enantiocontrol can be considered to be a function of trajectories **33**−**36** (Scheme 4, L = linker).[3] Although the absolute stereochemistries of *E*-**18** and *E*-**22** have not been determined, results from intermolecular cyclopropanation, which suggest that Cu(I)/**10** yields (1*R*,2*R*)-**3** and that chiral rhodium(II) carboxamidates **7**−**9** produce **3** in the

Scheme 4



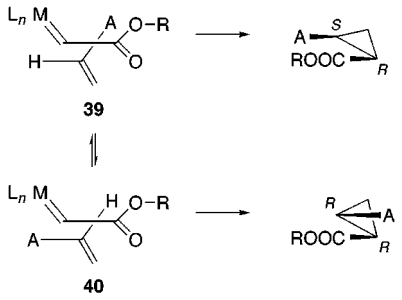
Scheme 5



predominant (1*S*,2*S*)-configuration,[4,12,28] implicate either **33** and **34** or **35** and **36**. If the anti-alignment of metal and carbonyl is preferred for the intermolecular reaction, then chiral dirhodium(II) carboxamidate catalysts prefer **33** and Cu(I)/**10**, **5**, and *ent*-**6** prefer **34**. The positioning of the carbon−carbon double bond on a specific trajectory to the metal carbene center is obviously a function of the chiral ligands on the metal and conformational preferences in the reacting substrate.

Why then does intermolecular cyclopropanation give configurational preference that is opposite to that from intramolecular cyclopropanation? The answer, we believe, lies in the trajectories of the alkene with respect to the carbene. Consider first the alignment depicted in Scheme 5 for reactions catalyzed by chiral dirhodium carboxamidates **7**−**9**. Here the alkene substituent is oriented

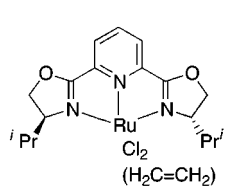
Scheme 6

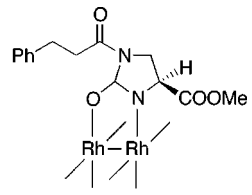


away from the metal and from OR. Notice that increasing the size of L_nM favors **37** over **38** and should lead to increased cis-selectivity, and this is what has been observed.[29] Increasing the size of R should lead to a modest increase in trans-selectivity, and this is also what has been observed.[4,15]

The alternative alignment is that depicted in Scheme 6 for reactions catalyzed by Cu(I)/**10**. Here the alkene substituent lies close to or far away from R, so that increasing the size of R should have a dramatic influence on the diastereomer ratio. As predicted, increasing the size of R increases trans-selectivity directly and substantially.[11]

This mechanistic treatment provides a new level of understanding for considerations of enantiocontrol in cyclopropanation reactions. First of all, that dirhodium(II) carboxamidates **7**-**9** react primarily through **29**, and that Cu(I)/**10** operates primarily through **30**, in intramolecular cyclopropanation reactions offers a predictive interpretation of the outcome of a vast array of intramolecular reactions already reported as well as those not yet performed. That the preference for **30** is not solely a function of C_2-symmetric ligands such as **10** can be seen in that (pybox)$RuCl_2$(ethene) (**41**) appears to operate via **29**,[30] and with such a late transition state that methallyl diazoacetate does not undergo intramolecular cyclopropanation.[14] Furthermore, the design of Rh_2(4*S*-MPPIM)$_4$ (**42**) as a catalyst makes possible mechanistic preference for **30** in reactions with 2-substituted allyl diazoacetates[31] not possible with **7**−**9**.





A second consideration made possible by this mechanistic treatment is the recognition that the preferred configuration for the *cis*(*Z*)-isomer formed by intermolecular cyclopropanation may be opposite of that formed by intramolecular cyclopropanation. This is, in fact, the case for Cu(I)/**10**, **5**, *ent*-**6**, and **7**−**9**, and this observation explains why, in the limit as ring size increases, enantiomeric excess for the *cis(Z)*-isomer does not approach

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that of *cis*-**3**. However, with use of **41** cyclopropane products having the same absolute configuration are obtained whether intermolecular or (from a limited data set) intramolecular cyclopropanation occurs.[30]

Last, consideration of the trajectories of Schemes 5 and 6 begins to suggest the *trans*(*E*)-preference from the vast array of copper(I) cyclopropanation catalysts,[4,5,15] especially from **40**, and the *cis*(*Z*)-preference of dirhodium(II) carboxamidates[29] (from **37** where the substituent of the alkene (A) is located away from the ligated metal; compare with **38**). However, the determination of whether absolute configuration is maintained in the *trans*(*E*)-substituted cyclopropane series from catalytic intermolecular to intramolecular cyclopropanation awaits discovery, as does the question of whether the carbonyl group of the intermediate carbene lies syn or anti to the ligated metal. So also will be the determination of configurational preference in intramolecular cyclopropanation reactions from the recently reported metal-salen catalysts.[32]

Experimental Section

General Methods. ^{1}H NMR (250, 300 or 500 MHz) and ^{13}C NMR (62.5, 75 or 125 MHz) spectra were obtained from solutions in $CDCl_3$, and chemical shifts are reported in parts per million (ppm, δ) downfield from the internal standard, Me_4-Si (TMS). Mass spectra were obtained using electron ionization on a quadrupole instrument. Infrared spectra were recorded as indicated, either as a thin film on sodium chloride plates or as solutions; absorptions are reported in wavenumbers (cm^{-1}). Anhydrous THF was distilled over sodium/benzophenone ketyl, and dichloromethane was distilled over calcium hydride. Methanesulfonyl azide was prepared by reaction of methanesulfonyl chloride with sodium azide and was not distilled.[33] $Cu(MeCN)_4PF_6$[34] and Rh_2(4*S*-IBAZ)$_4$,[8] Rh_2(5*S*-MEPY)$_4$,[9] Rh_2(4*R*-MEOX)$_4$[10] were prepared as previously described. The preparation of **2** and Rh_2(4*R*-dFIBAZ)$_4$ is being reported separately from this contribution.[35] The preparation of bis-oxazoline **10** followed the literature description.[36]

General Procedure for the Reaction of Ethyl Diazoacetate with Allyl Ethyl Ether. A solution of ethyl diazoacetate (0.165 g, 1.50 mmol) in 10 mL of CH_2Cl_2 was added via a syringe pump (5.0 mL/h) over 2 h to a refluxing solution of $Cu(MeCN)_4PF_6$ (5.6 mg, 0.015 mmol) and allyl ethyl ether (1.29 g, 15.0 mmol) in 10 mL of CH_2Cl_2. After complete addition the reaction mixture was stirred at reflux for an additional 1 h to ensure complete reaction. The reaction mixture was cooled to room temperature, then passed through a short silica plug, which was subsequently washed with CH_2Cl_2 (20 mL). The solvent was removed under reduced pressure to produce 0.225 g of products (87% yield) consisting a mixture of **3** and **4**. The crude products were subjected to GC on a 30-m SPB-5 column for the determination of the relative ratio of **3*Z***, **3*E*** and **4**. Enantioselectivites of the products were determined by GC on a 30-m Chiraldex B-DM column. Column chromatography on silica gel (hexanes/ethyl acetate = 20:1) yielded 92 mg of *Z*/*E* mixture **3** (37% yield) and 38 mg of **4** (15% yield). **3*Z***: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.18−4.08 (comp, 2H), 3.73 (dd, J = 10.3, 6.0 Hz, 1H), 3.49 (q, J = 7.0 Hz, 2H), 3.45 (dd, J = 10.3, 9.6 Hz, 1H), 1.80 (ddd, J = 8.6, 7.8, 5.8 Hz, 1H), 1.58 (comp, 1H), 1.27 (t, J = 7.2 Hz, 3H), 1.17 (t, J = 7.0 Hz, 3H), 1.11−1.05 (comp, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.4, 68.2, 65.9, 60.3, 20.8, 17.5, 15.2, 14.2, 11.7; GC on a 30-m SPB-5 column: t_R 8.22 min (flow rate: 1 mL/min, oven temp: 100 °C for 2 min then 10 °C/min to 275 °C), GC on a 30-m Chiraldex B-DM column: t_R 51.7 and 54.1 min (flow rate: 1 mL/min, oven temp: 70 °C for 30 min then 0.5 °C/min to 80 °C). **3*E***: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.18−4.08 (comp, 2H), 3.49 (q, J = 7.0 Hz, 2H), 3.37 (dd, J = 10.4, 7.1 Hz, 1H), 3.34 (dd, J = 10.4, 6.5 Hz, 1H), 1.72 (ddddd, J = 8.3, 7.1, 6.5, 4.8, 4.0 Hz, 1H), 1.53 (ddd, J = 8.8, 6.3, 4.0 Hz, 1H), 1.26 (t, J = 7.1 Hz, 3 H), 1.20 (t, J = 7.1 Hz, 3 H), 1.19 (ddd, J = 8.8, 4.8, 4.3 Hz, 1H), 0.85 (ddd, J = 8.3, 6.3, 4.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.7, 72.0, 66.0, 60.4, 21.6, 18.5, 15.1, 14.1, 12.9; GC on a 30-m SPB-5 column: t_R 8.57 min (flow rate: 1 mL/min, oven temp: 100 °C for 2 min then 10 °C/min to 275 °C), GC on a 30-m Chiraldex B-DM column: t_R 57.9 and 59.5 min (flow rate: 1 mL/min, oven temp: 70 °C for 30 min then 0.5 °C/min to 80 °C). **4**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.83 (ddt, J = 13.9, 10.3, 7.1 Hz, 1H), 5.12 (dd, J = 17.9, 1.7 Hz, 1H), 5.07 (dd, J = 10.5, 1.7 Hz, 1H), 4.25−4.18 (comp, 2H), 3.89 (t, J = 6.6 Hz, 1H), 3.64 (dt, J = 9.3, 7.1 Hz, 1H), 3.44 (dt, J = 9.3, 7.1 Hz, 1H), 2.48 (dd, J = 7.1, 6.6 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.3, 133.5, 117.7, 78.5, 65.9, 60.7, 37.3, 15.0, 14.2; MS (EI): m/z 173 (M + 1); IR ($CDCl_3$) 1742 (C=O), 1645 (C=C) cm^{-1}; GC on a 30-m SPB-5 column: t_R 6.35 min (flow rate: 1 mL/min, oven temp: 100 °C for 2 min then 10 °C/min to 275 °C), GC on a 30-m Chiraldex B-DM column: t_R 21.5 and 23.4 min (flow rate: 1 mL/min, oven temp: 70 °C for 30 min then 0.5 °C/min to 80 °C). For cyclopropanes **3*E*** and **3*Z*** the major enantiomers eluted second from Chiraldex B-DM columns for catalysis by **7**−**9** and first for catalysis Cu(I)/**10**, **5**, and *ent*-**6**. For **4** the major enantiomer eluted second with Cu(I)/**10** and *ent*-**6**. The racemates of **3** and **4** have been reported.[37]

2-Allyloxyethyl Diazoacetate (13) was prepared by the same procedure as described for the preparation of diazo compound **21** by using 2-allyloxyethanol as the starting material (65% yield): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.91 (ddt, J = 17.4, 10.5, 5.7 Hz, 1H), 5.28 (ddt, J = 17.4, 1.8, 1.2 Hz, 1H), 5.19 (ddt, J = 10.5, 10.3, 5.7 Hz, 1H), 4.81 (br s, 1H), 4.40−4.25 (comp, 2H), 4.03 (dt, J = 5.7, 1.2 Hz, 2H), 3.72−3.61 (comp, 2H); ^{13}C ($CDCl_3$, 62.5 MHz) δ (C=O not observed), 134.3, 117.3, 72.0, 67.8, 63.9; HRMS calcd for $C_7H_{11}N_2O_3$ 171.0770, found 171.0773; IR ($CDCl_3$) 2117 (C=N$_2$), 1700 (C=O) cm^{-1}.

Diazo Decomposition of 13. To a refluxing solution of Rh_2(OAc)$_4$ (1.8 mg, 0.0040 mmol) in CH_2Cl_2 (2.0 mL) was added diazoacetate **13** (68.0 mg, 0.40 mmol) in 2 mL of CH_2Cl_2 over 2 h via a syringe pump. The reaction mixture was refluxed for an additional half hour to complete the reaction. After cooling to room temperature, the reaction mixture was filtered through a short plug of silica gel, and the solvent was removed under reduced pressure to provide 53 mg (93% yield) of crude product as a colorless oil which contained **14**−**16** and dimer. Relative yield of the crude product was determined by GC on a 30-m SPB-5 column. The Rh_2(*S*-TBPRO)$_4$-catalyst catalyzed reaction of **13** gave 54 mg crude product (95% crude yield), from which 33 mg authentic cyclopropane product **14** was isolated (58% yield) after column chromatography (hexanes/ethyl acetate = 10:1). Using the same procedure, the C−H insertion product **15** (46 mg, 81% yield) was isolated from the reaction catalyzed by Rh_2(4*R*-MEOX)$_4$, and the ylide product **16** (42 mg, 74% yield) was obtained from the $CuPF_6$/**10**-catalyzed reaction. **3,6-Dioxabicyclo[6.1.0]nonan-2-one (14)**: $[\alpha]^{26}_D$ = −0.6 for 33% ee (c = 1.0, CH_2Cl_2) from reaction of **13** with Rh_2(*S*-DOSP)$_4$;[38] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.02 (ddd, J = 13.5, 8.6, 1.0 Hz, 1H), 4.39 (dd, J = 13.2, 3.8 Hz, 1H), 4.21 (ddd, J = 13.5, 4.2, 1.0 Hz, 1H), 4.03 (ddd, J = 14.2,

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(38) Reaction gave results nearly identical with those reported in Table 3 (**14**: **15**: **16** = 86:10:4) with 33% ee for **14**, 26% ee for **15**, and 18% ee for **16**. For details of Rh_2(*S*-DOSP)$_4$ reactions see: Davies, H. M. L. *Eur. J. Chem.* **1999**, 7919.

4.2, 1.0 Hz, 1H), 3.73 (ddd, J = 14.2, 8.6, 1.0 Hz, 1H), 2.81 (dd, J = 13.2, 10.0 Hz, 1H), 1.89 (td, J = 8.7, 5.6 Hz, 1H), 1.67 (dtdd, J = 10.0, 8.7, 5.6, 3.8 Hz, 1H), 1.14 (td, J = 8.7, 5.6 Hz, 1H), 0.88 (td, J = 5.8, 5.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (C=O not observed), 72.4, 71.3, 70.1, 20.2, 18.9, 8.3; HRMS calcd for $C_7H_{13}O_3$ 143.0708, found 143.0702; IR ($CDCl_3$) 1727 (C=O) cm^{-1}; GC on a 30-m SPB-5 column: t_R 10.03 min (flow rate: 1 mL/min, oven temp: 100 °C for 2 min then 10 °C/min to 275 °C); GC on a 30-m Chiraldex B-DM column: t_R 74.3 and 76.9 min (flow rate: 1 mL/min, oven temp: 90 °C for 40 min then 1 °C/min to 140 °C). The predominant enantiomer from reactions catalyzed by Cu(I)/**10**, **5**, and *ent*-**6** eluted first on a Chiraldex G-TA column, opposite to that for **14** from the reaction catalyzed by **7**. **4-Allyloxydihydrofuran-2-one (15)**: $[\alpha]^{26}_D$ = +45.1 for 96% ee (c = 2.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.89 (ddt, J = 17.1, 10.4, 5.5 Hz, 1H), 5.31 (ddt, J = 17.1, 1.5, 1.4 Hz, 1H), 5.23 (ddt, J = 10.4, 1.5, 1.4 Hz, 1H), 4.39 (dd, J = 10.2, 4.5 Hz, 1H), 4.37 (dd, J = 10.2, 1.2 Hz, 1H), 4.35 (comp, 1H), 4.02 (ddt, J = 12.7, 5.5, 1.4 Hz, 1H), 3.99 (ddt, J = 12.7, 5.5, 1.4 Hz, 1H), 2.70 (dd, J = 17.9, 6.2 Hz, 1H), 2.60 (dd, J = 17.9, 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.5, 133.6, 117.8, 73.8, 73.1, 69.9, 34.9; HRMS calcd for $C_7H_{13}O_3$ 143.0708, found 143.0710; IR ($CDCl_3$): 1782 (C=O) cm^{-1}; GC on a 30-m SPB-5 column: t_R 9.29 min (flow rate: 1 mL/min, oven temp: 100 °C for 2 min then 10 °C/min to 275 °C), GC on a 30-m Chiraldex G-TA column: t_R 39.5 and 41.2 min (flow rate: 1 mL/min, oven temp: 100 °C). The predominant enantiomer from reactions catalyzed by Cu(I)/**10**, **5**, and *ent*-**6** eluted first on the Chiraldex G-TA column, opposite to that for **15** from the reactions catalyzed by **7**−**9**. **3-Allyl-(1,4)-dioxan-2-one (16)**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.87 (ddt, J = 17.1, 10.1, 6.8 Hz, 1H), 5.21 (dq, J = 17.1, 1.4 Hz, 1H), 5.16 (dq, J = 10.1, 1.4 Hz, 1H), 4.54 (ddd, J = 12.7, 10.1, 3.4 Hz, 1H), 4.42 (ddd, J = 12.7, 3.4, 2.5 Hz, 1H), 4.39 (dd, J = 8.5, 3.8 Hz, 1 H), 4.00 (ddd, J = 12.7, 2.7, 2.5 Hz, 1 H), 3.85 (ddd, J = 12.7, 10.1, 2.7 Hz, 1H), 2.72 (comp, 1H), 2.66 (comp, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.5, 132.8, 118.7, 76.4, 68.8, 62.4, 36.5; MS (EI): m/z 143 (M+1, 100), 99 (6), 73 (31); IR ($CDCl_3$): 1742 (C=O), 1647 (C=C) cm^{-1}; GC on a 30-m SPB-5 column: t_R 8.32 min (flow rate: 1 mL/min, oven temp: 100 °C for 2 min then 10 °C/min to 275 °C), GC on a 30-m Chiraldex B-DM column: t_R 47.9 and 52.8 min (flow rate: 1 mL/min, oven temp: 90 °C for 40 min then 1 °C/min to 140 °C). The predominant enantiomer from reactions catalyzed by Cu(I)/**10**, **5**, and *ent*-**6** eluted first on a Chiraldex G-TA column, opposite to that for **16** from the reaction catalyzed by **9**. Compound **16** underwent decomposition on standing; TOCSY analysis was consistent with the assigned structure.

2-(2-Allyloxyethoxy)ethanol was prepared by the same procedure described for the preparation of [2-(2-allyloxyethoxy)ethoxy]ethanol except using diethylene glycol instead of triethylene glycol as starting material (70% yield): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.93 (ddt, J = 17.2, 11.7, 5.7 Hz, 1H), 5.28 (dq, J = 17.2, 1.5 Hz, 1H), 5.20 (dq, J = 11.7, 1.5 Hz, 1H), 4.03 (dt, J = 5.7, 1.5 Hz, 2H), 3.80−3.58 (comp, 8H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 134.4, 117.2, 72.5, 72.1, 70.3, 69.3, 61.6.

2-(2-Allyloxyethoxy)ethyl diazoacetate (17) was prepared according to the same procedure described for the preparation of diazo compound **21** (57% yield). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.93 (ddt, J = 17.2, 11.7, 5.7 Hz, 1H), 5.28 (dq, J = 17.2, 1.5 Hz, 1H), 5.20 (dq, J = 11.7, 1.5 Hz, 1H), 4.80 (s, 1H), 4.35−4.30 (comp, 2H), 4.03 (dt, J = 5.7, 1.5 Hz, 2H), 3.76−3.69 (comp, 2H), 3.69−3.54 (comp, 4H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ (C=O not observed), 134.6, 117.1, 72.2, 70.6, 69.4, 69.3, 63.9; IR ($CDCl_3$) 2123 (C=N$_2$), 1697 (C=O), 1455 (C=C) cm^{-1}; HRMS calcd for $C_9H_{15}O_4N_2$ 215.1032, found 215.1036.

Diazo decomposition of 17 proceeded via the same procedure described for diazo decomposition of **13**. $Rh_2(OAc)_4$ catalyst gave a *Z*/*E* mixture of **18** in a 73% isolated yield after column chromatography on silica gel (hexanes/ethyl acetate = 4:1) and C−H insertion product **19** was obtained by Rh_2(4*R*-MEOX)$_4$ catalysis in 70% yield. **Trioxabicyclo[9.1.0]-dodecan-2-one (18)**: IR ($CDCl_3$) 1720 (C=O) cm^{-1}; for *Z*-**18**: $[\alpha]^{28}_D$ = +11.7 for 59% ee (c = 1.3, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.67 (ddd, J = 10.0, 7.0, 2.5 Hz, 1H), 4.11 (dd, J = 10.0, 5.0 Hz, 1H), 4.03 (ddd, J = 8.0, 5.5, 2.5 Hz, 1H), 3.97 (ddd, J = 8.0, 5.5, 2.5 Hz, 1H), 3.73−3.66 (comp, 2H), 3.58−3.50 (comp, 2H), 3.38−3.29 (comp, 1H), 3.17 (t, J = 10.0 Hz, 1H), 1.93 (ddd, J = 9.0, 7.5, 6.0 Hz, 1H), 1.71−1.61 (comp, 1H), 1.20 (dt, J = 6.0, 5.5 Hz, 1H), 1.04 (ddd, J = 8.0, 7.5, 5.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.2, 71.7, 70.8, 69.6, 69.5, 63.3, 20.7, 18.4, 10.8; GC/MS (EI): m/z 187 (M + 1) (19), 158 (6), 143 (9), 99 (100); GC on a 30-m SPB-5 column: t_R 12.81 min (flow rate: 1.0 mL/min, oven temp: 100 °C for 2 min then 10 °C/min to 275 °C), GC on a 30-m Chiraldex B-TA column: t_R 31.6 (major isomer with **7**−**9**; minor isomer with CuC(I)/**10**, **5**, and *ent*-**6**) and 32.4 min (flow rate: 1 mL/min, oven temp: 120 °C); ***E*-18** from the reaction of **17** catalyzed by **5**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.02 (ddd, J = 12.0, 10.5, 3.0 Hz, 1H), 4.41−4.30 (comp, 2H), 4.03 (dd, J = 12.5, 4.0, 1H), 3.88 (ddd, J = 12.5, 3.5, 1.5 Hz 1H), 3.78−3.72 (comp, 2H), 3.56−3.50 (comp, 2H), 2.88 (dd, J = 12.5, 11.0 Hz, 1H), 1.81 (ddd, J = 7.5, 5.5, 4.5 Hz, 1H), 1.64−1.50 (comp, 2H), 0.91 (ddd, J = 7.5, 6.0, 4.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.2, 73.1, 72.6, 71.5, 68.2, 64.7, 27.0, 20.7, 12.4; GC/MS (EI): m/z 187 (M + 1) (3), 158 (5), 143 (20), 99 (100); GC on a 30-m SPB-5 column: t_R 12.97 min (flow rate: 1 mL/min, oven temp: 100 °C for 2 min then 10 °C/min to 275 °C), GC on a 30-m Chiraldex B-TA column: t_R 38.9 (minor isomer with **7**−**9**; major isomer with Cu(I)/**10**, **5**, and *ent*-**6**) and 42.0 min (flow rate: 1.0 mL/min, oven temp: 120 °C). **4-(2-Allyloxy)ethoxy-dihydrofuran-2-one (19)**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.93 (ddt, J = 17.2, 11.7, 5.7 Hz, 1H), 5.28 (dq, J = 17.2, 1.5 Hz, 1H), 5.20 (dq, J = 11.7, 1.5 Hz, 1H), 4.41−4.35 (comp, 3H), 4.03 (dt, J = 5.7, 1.5 Hz, 2H), 3.68−3.55 (comp, 4H), 2.69, 2.61 (AB system, J_{AB} = 14.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 175.5, 134.4, 117.3, 75.0, 73.2, 72.3, 69.4, 68.8, 35.0; IR (CH_2Cl_2) 1783 (C=O) cm^{-1}; HRMS calcd for $C_9H_{15}O_4$ 187.0970, found 187.0978; GC on a 30-m SPB-5 column: t_R 13.8 min (flow rate: 1 mL/min, oven temp: 100 °C for 2 min then 10 °C/min to 275 °C), GC on a 30-m Chiraldex B-TA column: t_R 40.5 (major isomer with Cu(I)/**10**, **5**, and *ent*-**6**) and 44.0 min (flow rate: 1.0 mL/min, oven temp: 150 °C).

Cyclopropane isomer *Z*-**18** was produced from the corresponding cyclopropene product formed by intramolecular cyclopropenation of 2-(2-propargyloxyethoxy)ethyl diazoacetate using Rh_2(4*S*-IBAZ)$_4$ as the catalyst. Catalytic reduction with H_2 over 10% Pd/C in ethyl acetate formed only ***Z*-18** which was analyzed to have 59% ee. Since a very similar cyclopropenation process was demonstrated to produce the (1*R*)-enantiomer with S-configured dirhodium(II) carboxamidate catalysts,[39] we assign ***Z*-18** formed with catalyst **7** to have the (1*R*,11*S*)-configuration since the predominant cyclopropane enantiomer formed by hydrogenation of the cyclopropene product: $[\alpha]^{28}_D$ = −131.3 (c = 1.0, CH_2Cl_2), and by cyclopropanation with Rh_2(4*S*-IBAZ)$_4$ were the same.

2-[2-(2-Allyloxyethoxy)ethoxy]ethanol. To an anhydrous THF (500 mL) solution of potassium *tert*-butoxide (2.3 g, 19.5 mmol) was added triethylene glycol (4.9 mL, 37.0 mmol) at room temperature. The resulting mixture was stirred for half an hour, after which was added allyl iodide (1.8 mL, 19.7 mmol) in 60 mL of THF over 1 h. After being stirred at room temperature for 24 h, the reaction mixture was filtered though a Celite plug (20 g), and the solvent was evaporated. The residue was subjected to column chromatography, eluting with ethyl acetate to give the title compound as a colorless oil (3.2 g, 86% yield): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.86 (ddt, J = 17.2, 10.3, 5.7 Hz, 1H), 5.21 (ddt, J = 17.2, 1.8, 1.2 Hz, 1H), 5.13 (ddt, J = 10.3, 10.3, 5.7 Hz, 1H), 3.97 (dt, J = 5.7, 1.2 Hz, 2H), 3.67−3.52 (comp, 13 H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 134.5, 117.1, 72.4, 72.1, 70.5, 70.4, 70.2, 69.2, 61.6; MS (FAB$^+$) m/z 191.1 (M + 1); IR (neat) 3434 (OH), 1645 (C=C) cm^{-1}.

2-[2-(2-Allyloxyethoxy)ethoxy]ethyl Diazoacetate (21). A solution of 2-[2-(2-allyloxyethoxy)ethoxy]ethanol (2.5 g, 13

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mmol) in 50 mL of THF was treated with triethylamine (0.36 mL, 2.6 mmol) and diketene (1.22 g, 14.5 mmol) at 0 °C. The solution was allowed to warm to room temperature and stirred for an additional 4 h. The solution was cooled to 0 °C again, and triethylamine (1.82 mL, 13.2 mmol) was added, followed by addition of methanesulfonyl azide (1.76 g, 14.5 mmol). The reaction solution was allowed to warm to room temperature, and stirring was continued for 15 h after which the solvent was removed under reduced pressure. The residue was dissolved in 100 mL of ethyl acetate, then washed with H_2O (50 mL) and brine (30 mL) and then the solvent was evaporated under reduced pressure. The crude diazoacetoacetate was purified by flash chromatography on silica gel (hexanes/ethyl acetate = 2:1) and then dissolved in THF (20 mL). The THF solution was cooled to 0 °C and followed by addition of LiOH (1.1 g, 46.2 mmol) in H_2O (20 mL). The reaction mixture was allowed to stir at room temperature for 1 h. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layer was washed with brine, and the solvent was evaporated under reduced pressure. Purification by column chromatography (hexanes/ethyl acetate = 2:1) yielded product **21** as a yellow oil (1.7 g, 50% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.92 (ddt, J = 17.4, 10.5, 5.7 Hz, 1H), 5.28 (ddt, J = 17.4, 1.8, 1.2 Hz, 1H), 5.18 (ddt, J = 10.5, 10.3, 5.7 Hz, 1H), 4.81 (br s, 1H), 4.32 (t, J = 4.8 Hz, 2H), 4.03 (dt, J = 5.7, 1.2 Hz, 2H), 3.68−3.45 (comp, 10 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.7, 134.7, 117.0, 72.2, 70.6, 70.5, 69.4, 69.2, 63.9, 46.3; MS (FAB$^+$) m/z 259.1 (M + 1); IR (neat) 2114 (C═N_2), 1682 (C═O) cm^{-1}.

Diazo Decomposition of 21. To a refluxing solution of catalyst (1 mol %) in 4 mL of CH_2Cl_2 was added **21** (51.6 mg, 0.200 mmol) in 2 mL of CH_2Cl_2 over 2 h via a syringe pump. The reaction mixture was refluxed for an additional half hour to complete the reaction. After cooling to room temperature, the reaction mixture was subjected to column chromatography on silica gel (hexanes/ethyl acetate = 1:2) to yield a colorless oil. The product ratios and ee values were determined by GC analysis on a 30-m Chiraldex B-PH column. The $Rh_2(OAc)_4$-catalyzed reaction of **21** yielded cyclopropane product **22** (29 mg, 63% yield). The C−H insertion product **23** (25 mg, 54% yield) was isolated from the product mixture catalyzed by Rh_2-(5*S*-MEPY)$_4$, and the ylide product **24** (5 mg, 11% yield) was obtained from the $CuPF_6$ catalyzed reaction. **3,6,9,12-Tetraoxabicyclo[12.1.0]pentadecan-2-one (22)**: HRMS calcd for $C_{11}H_{19}O_5$ 231.1232, found 231.1226; IR ($CDCl_3$) 1720 (C═O) cm^{-1}. for ***Z*-22**: $[\alpha]^{28}_D$ = +2.5 for 78% ee (c = 2.2, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.76 (ddd, J = 11.8, 8.3, 1.6 Hz, 1H), 3.89 (dd, J = 10.2, 5.3 Hz, 1H), 3.87 (comp, 1H), 3.76−3.44 (comp, 10H), 3.38 (t, J = 10.2 Hz, 1H), 1.90 (ddd, J = 8.2, 8.0, 5.6 Hz, 1H), 1.68 (dtdd, J = 10.2, 8.2, 5.6, 5.3 Hz, 1H), 1.12 (ddd, J = 5.6, 5.2, 4.8 Hz, 1H), 1.07 (ddd, J = 8.2, 8.0, 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.4, 70.8, 70.4, 69.9, 69.8, 69.3, 68.8, 63.5, 21.2, 17.7, 11.1; GC on a 30-m SPB-5 column: t_R 16.11 min (flow rate: 1 mL/min, oven temp: 100 °C for 2 min then 10 °C/min to 275 °C), GC on a 30-m Chiraldex B-PH column: t_R 86.2 (minor isomer from reactions catalyzed by **7**−**9**; major isomer from reactions catalyzed by Cu(I)/**10**, **5**, and *ent*-**6**) and 88.3 min (flow rate: 1 mL/min, oven temp: 150 °C); for ***E*-22** from the reaction of **21** catalyzed by **9**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.70 (dt, J = 11.5, 4.5 Hz, 1H), 4.02 (dd, J = 12.6, 4.0 Hz, 1H), 4.00 (dt, J = 12.0, 4.5 Hz, 1H), 3.76−3.44 (comp, 10H), 2.84 (dd, J = 12.6, 10.4 Hz, 1H), 1.78 (comp, 1H), 1.76 (ddd, J = 9.4, 6.3, 4.8 Hz, 1H), 1.35 (dt, J = 9.4, 4.8 Hz, 1H), 0.73 (ddd, J = 8.0, 6.3, 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.9, 73.2, 71.0, 70.9, 70.1, 69.2, 68.7, 62.8, 23.3, 20.0, 11.8; GC on a 30-m SPB-5 column: t_R 16.11 min (flow rate: 1 mL/min, oven temp: 100 °C for 2 min then 10 °C/min to 275 °C), GC on a 30-m Chiraldex B-PH column: t_R 89.3 (minor isomer from reactions catalyzed by **7**−**9**; major isomer from reactions catalyzed by Cu(I)/**10**, **5**, and *ent*-**6**) and 91.8 min (flow rate: 1 mL/min, oven temp: 150 °C). **4-[2-(2-Allyloxyethoxy)-ethoxy]dihydrofuran-2-one (23):** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.92 (ddt, J = 17.3, 10.4, 5.7 Hz, 1H), 5.29 (dq, J = 17.3, 1.5 Hz, 1H), 5.20 (dq, J = 10.4, 1.5 Hz, 1H), 4.40 (dd, J = 8.5, 5.5 Hz, 1H), 4.38 (dd, J = 8.5, 2.5 Hz, 1H), 4.03 (dt, J = 5.7, 1.5 Hz, 2H), 3.75−3.59 (comp, 9H), 2.70 (dd, J = 16.5, 5.5 Hz, 1H), 2.62 (dd, J = 16.5, 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.6, 134.5, 117.3, 75.0, 73.2, 72.2, 70.7, 70.6, 69.3, 68.7, 35.0; HRMS calcd for $C_{11}H_{19}O_5$: 231.1232, found: 231.1239; IR ($CDCl_3$): 1779 (C═O) cm^{-1}; GC on a 30-m SPB-5 column: t_R 16.56 min (flow rate: 1 mL/min, oven temp: 100 °C for 2 min then 10 °C/min to 275 °C). Enantiomer separation could not be achieved on Chiraldex TA, PH, or DM chiral columns. **3-Allyl-1,4,7,10-tetraoxacyclodecan-2-one (24).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.84 (ddt, J = 17.0, 10.0, 6.8 Hz, 1H), 5.15 (ddt, J = 17.0, 1.5, 1.2 Hz, 1H), 5.09 (ddt, J = 10.1, 1.5, 1.2 Hz, 1H), 4.50 (ddd, J = 12.0, 6.1, 2.7 Hz, 1H), 4.19 (ddd, J = 11.8, 6.5, 2.7 Hz, 1H), 3.98 (t, J = 6.8 Hz, 2H), 3.95−3.48 (comp, 9H), 2.48 (tt, J = 6.5, 1.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.2, 133.9, 118.5, 81.3, 72.1, 71.9, 71.7, 70.5, 69.3, 64.1, 38.3; GC on a 30-m SPB-5 column: t_R 14.72 min (flow rate: 1 mL/min, oven temp: 100 °C for 2 min then 10 °C/min to 275 °C), GC on a Chiraldex B−PH column: t_R 36.6 (major isomer from the reaction catalyzed by Cu(I)/**10**) and 38.5 min (flow rate: 1 mL/min, oven temp: 150 °C).

Cyclopropane isomer *Z*-**22** was produced from the corresponding cyclopropene product formed by intramolecular cyclopropenation of 2-[2-(2-propargyloxyethoxy)ethoxy]ethyl diazoacetate using Rh_2(4*S*-IBAZ)$_4$ as the catalyst, and analyses were performed as previously described for *Z*-**18**. The cyclopropene product, $[\alpha]^{28}_D$ = −31.6 (c = 2.1, CH_2Cl_2), was subjected to catalytic hydrogenation with 10% Pd/C in ethyl acetate to form only *Z*-**22**. The absolute configuration of the major enantiomer of this product and that from **21** using Rh_2-(4*S*-IBAZ)$_4$ were the same, prompting our assignment of (1*R*,-14*S*)-**22** to be the absolute configuration of the major enantiomer formed from catalysis by **7**−**9**.

Acknowledgment. We are grateful to the National Science Foundation and to the National Institutes of Health (GM 46503) for their support of this research. We wish to thank Andrew Wee for helpful mechanistic discussions.

Supporting Information Available: Carbon and proton spectra for reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

JO005589Z