Chiral Catalyst Controlled Diastereoselection and Regioselection in Intramolecular Carbon−Hydrogen Insertion Reactions of Diazoacetates

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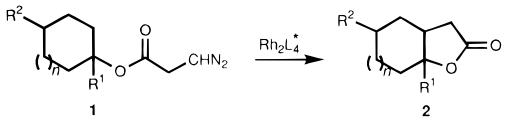
Abstract: Individual enantiomers of substituted cyclohexyl diazoacetates or 2-octyl diazoacetates matched with a configurationally suitable chiral dirhodium(II) carboxamidate catalyst provide an effective methodology for the synthesis of lactones with exceptional diastereo- and regiocontrol. Enantiomerically pure (1*S*,2*R*)-*cis*-2-methylcyclohexyl diazoacetate forms the *all-cis*-(1*R*,5*R*,9*R*)-9-methyl-2-oxabicyclo[4.3.0]nonan-3-one with complete diastereocontrol in reactions catalyzed by dirhodium(II) tetrakis[methyl 1-(3-phenylpropanoyl)-2-oxoimidazolidine-4(*R*)-carboxylate], Rh_2(4(*S*)-MPPIM)$_4$, but the configurational mismatch results in a mixture of products. The same diazoacetate produces (1*S*,5*R*)-5-methyl-2-oxabicyclo[4.3.0]nonan-3-one with virtually complete selectivity by catalysis with dirhodium(II) tetrakis[methyl 2-oxopyrrolidine-5(*S*)-carboxylate], Rh_2(5(*S*)-MEPY)$_4$. Similarly high stereo- and regiocontrol is also achieved with enantiomerically pure *trans*-2-methylcyclohexyl diazoacetates. Product control from insertion reactions of *d*- or *l*-menthyl diazoacetate and (+)-neomenthyl diazoacetate from the configurational match with dirhodium(II) catalyst results in the formation of one C−H insertion product in high yield. The exceedingly high product diastereoselection observed in these reactions is consistent with virtually exclusive insertion into equatorial C−H bonds. The catalyst-dependent selective formation of a *cis*-disubstituted γ-butyrolactone or a β-lactone from 2-octyl diazoacetate has been achieved. Control of product diastereoselectivity and regioselectivity in C−H insertion reactions is explained by conformational suitability in configurational match/mismatch of catalyst and carbene.

Introduction

The dirhodium(II)-catalyzed intramolecular metal carbene C−H insertion transformation holds considerable promise as a useful methodology for organic synthesis.[1−5] However, with multiple sites for insertion, effective control of regioselectivity and stereoselectivity can be a challenge of unmistakable complexity. Preference exists for the formation of five-membered rings, and reactivity for insertion into C−H bonds follows the order tertiary > secondary ≫ primary.[6,7] Heteroatoms that include oxygen and nitrogen activate adjacent C−H bonds for insertion,[8−11] but conformational effects can and do override electronic preferences.[12] Diastereocontrol[11−15] and enantiocontrol[14−18] set further restrictions for this methodology.

We have recently communicated examples of exceptional diastereo- and enantiocontrol in intramolecular C−H insertion reactions of achiral cycloalkyl diazoacetates (eq 1, n = 0−3; R^1 = H, Me; R^2 = H, alkyl).[15] As many as four isomeric



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products could have arisen from insertion into the prochiral

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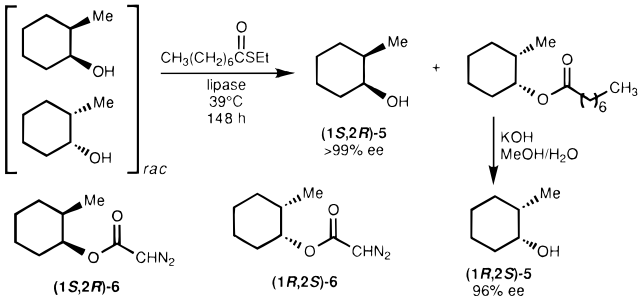
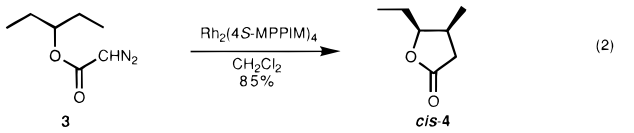
Scheme 1



C−H bonds β to the site of diazoacetate substitution, but with the use of select chiral dirhodium(II) carboxamidates as catalysts, C−H insertion has been directed to the formation of only one. With symmetric acyclic diazoacetates only one product has been produced from reactions catalyzed by $Rh_2(4(S)\text{-MPPIM})_4$ in high isolated yield (eq 2, 97:3 *cis/trans*, 99% ee ***cis*-4**).[19] However, as has been demonstrated in



(2)

cyclopropanation reactions of secondary allylic diazoacetates catalyzed by chiral dirhodium(II) carboxamidates,[20] individual enantiomers can produce different diastereoisomers with a high degree of selectivity when there is an optimum match of enantiomeric substrate and catalyst configuration. In C−H insertion reactions lower product yields and changes in both diastereocontrol and regioselectivity can accompany a substrate/catalyst configurational mismatch.[21] We report that individual enantiomers of substituted cyclohexyl or 2-octyl diazoacetates matched with a suitable chiral dirhodium(II) carboxamidate catalyst provide an effective methodology for the synthesis of lactones with exceptional diastereo- and regiocontrol.

Results

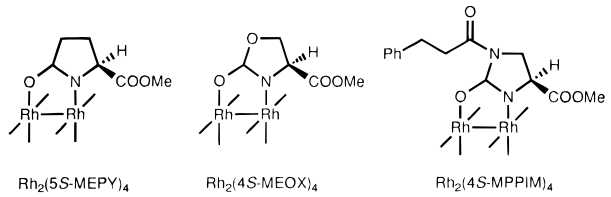
rac-cis-2-Methylcyclohexanol was resolved on a semipreparative scale with an immobilized triacyl glycerol lipase from *Candida antarctica* using *S*-ethyl thiooctanoate as the acyl donor (Scheme 1) according to the protocol of Hult and co-workers.[22] (1*S*,2*R*)-(+)-*cis*-2-Methylcyclohexanol **[(1*S*,2*R*)-5]** was separated from (1*R*,2*S*)-*cis*-2-methylcyclohexyl octanoate by distillation, and the ester was hydrolyzed to (1*R*,2*S*)-(−)-*cis*-2-methylcyclohexanol **[(1*R*,2*S*)-5]**. These alcohols were converted to their corresponding diazoacetates [**(1*S*,2*R*)-6** and (**1*R*,2*S*)-6**] by the standard methodology of condensation with diketene, diazo transfer with methanesulfonyl azide, and deacylation with LiOH in greater than 70% overall yield.[23,24] Diazo decomposition was accomplished using an optimized set of

Table 1. Product Distribution from Dirhodium(II)-Catalyzed Intramolecular C−H Insertion Reactions of *cis*-2-Methylcyclohexyl Diazoacetates (**6**)[a]

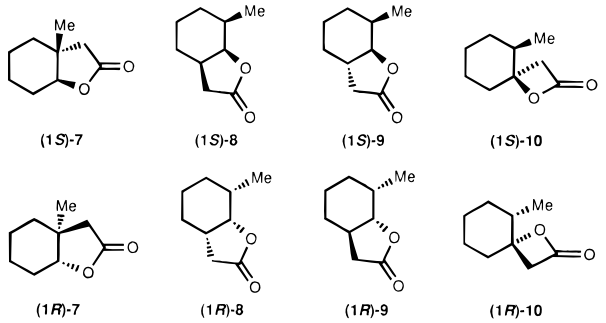
diazoacetate	catalyst	isolated yield, %[b]	relative yield, %			
			7	**8**	**9**	**10**
(1*S*,2*R*)-6[c]	$Rh_2(5(S)\text{-MEPY})_4$	95	94	1	t[g]	5
	$Rh_2(5(R)\text{-MEPY})_4$	79	4	91	3	2
	$Rh_2(4(S)\text{-MEOX})_4$	82	90	1	0	9
	$Rh_2(4(R)\text{-MEOX})_4$	91	2	88	7	3
	$Rh_2(4(S)\text{-MPPIM})_4$	46	28	16	t	56
	$Rh_2(4(R)\text{-MPPIM})_4$[d]	88	0	98	0	2
(1*R*,2*S*)-6*e***	$Rh_2(5(S)\text{-MEPY})_4$	86	5	90[f]	3	2
	$Rh_2(5(R)\text{-MEPY})_4$	74	92[f]	3	0	5
	$Rh_2(4(S)\text{-MEOX})_4$	89	2	88[f]	7	3
	$Rh_2(4(R)\text{-MEOX})_4$	86	88[f]	3	0	9
	$Rh_2(4(S)\text{-MACIM})_4$	90	1	96[f]	1	2
	$Rh_2(4(S)\text{-MPPIM})_4$	91	t	98[f]	t	2

[a] Reactions were performed in refluxing CH_2Cl_2 with 1.0 mol % catalyst, unless specified otherwise. [b] For C−H insertion products only. [c] >99% ee. [d] 0.1 mol % catalyst. [e] 96% ee. [f] ≥99% ee. [g] t = trace.

chiral dirhodium(II) carboxamidate catalysts consisting of dirhodium(II) tetrakis[methyl 2-oxopyrrolidine-5(*R* and *S*)-carboxylate], $Rh_2(5(R)\text{-MEPY})_4$ and $Rh_2(5(S)\text{-MEPY})_4$,[25] dirhodium(II) tetrakis[methyl 2-oxooxazolidine-4(*R* and *S*)-carboxylate], $Rh_2(4(R)\text{-MEOX})_4$ and $Rh_2(4(S)\text{-MEOX})_4$,[26] and dirhodium(II) tetrakis[methyl 1-(3-phenylpropanoyl)-2-oxoimidazolidine-4(*R* and *S*)-carboxylate], $Rh_2(4(R)\text{-MPPIM})_4$ and $Rh_2(4(S)\text{-MPPIM})_4$.[17a,27] Each of these catalysts is structurally well defined with two oxygen and two nitrogen donor atoms bound to each rhodium so that the resulting configuration is 2,2-*cis*.



Results from catalytic diazo decomposition of the diazoacetates derived from **(1*S*,2*R*)-5** and **(1*R*,2*S*)-5** using chiral dirhodium(II) carboxamidates in amounts as low as 0.1 mol % are recorded in Table 1. For each diazoacetate a total of four products was anticipated from C−H insertion, **7**−**10**, excluding



those from insertion into a methyl C−H bond or into a remote ring methylene C−H bond, neither of which were observed, but as can be seen from the data in Table 1, only two products in each set (**7** and **8**) are formed individually with specific

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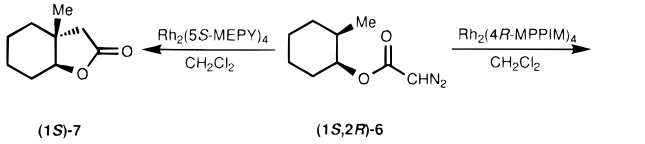
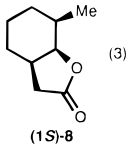
catalysts in synthetically meaningful yields and high diastereomeric ratios and/or regioselectivities (eqs 3 and 4). Since





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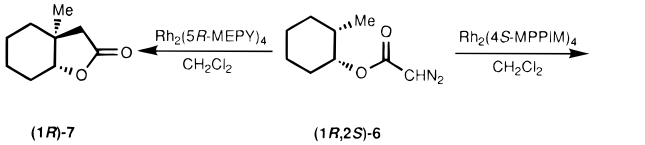
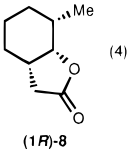


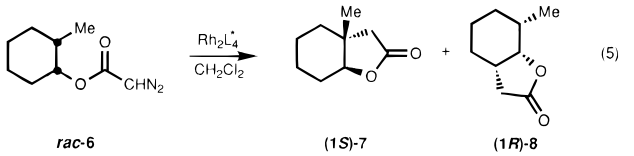


(4)

thermal decomposition of β-lactone **10** produces the volatile 2-methylcyclohexanone and 2-methylmethylenecyclohexane, removal of **10** from the composite is justified, and product selectivity calculated from **7**−**9** is >97:3 for **7** with $Rh_2(MEPY)_4$ catalysts and >99:1 for **8** with $Rh_2(MPPIM)_4$ catalysts. For comparison, the 1-acetyl analog of $Rh_2(4(S)\text{-MPPIM})_4$, $Rh_2(4(S)\text{-MACIM})_4$,[23] provided selectivity for the formation of **(1*R*)-8** that was 98:2.

The (*R*)-enantiomer of each set of catalysts is most selective for the formation of **(1*S*)-8** in reactions with **(1*S*,2*R*)-6** and most selective for **(1*S*)-7** in reactions with **(1*R*,2*S*)-6**. The mirror image of these results occurs with the use of the (*S*)-enantiomer of each catalyst. The one exception to this generalization is the $Rh_2(4(S)\text{-MPPIM})_4$-catalyzed diazo decomposition of **(1*S*,2*R*)-6** (Table 1) that produces a mixture in which β-lactone **10** is the major product, but low product yield was realized. Compound **10** is thermally unstable and, during GC analysis or product distillation, undergoes ketene or carbon dioxide extrusion to form 2-methylcyclohexanone or 2-methylmethylenecyclohexane, respectively.[28] Compounds **9** and **10** are apparently formed as a configurational mismatch of catalyst and diazoacetate.

When *rac-cis*-2-methylcyclohexyl diazoacetate was treated with $Rh_2(5(S)\text{-MEPY})_4$, the resultant products consisted of **(1*S*)-7** and **(1*R*)-8** (eq 5) as well as minor amounts of **9** (2%)

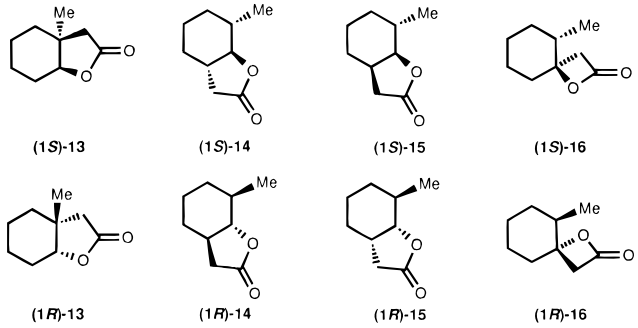


(5)

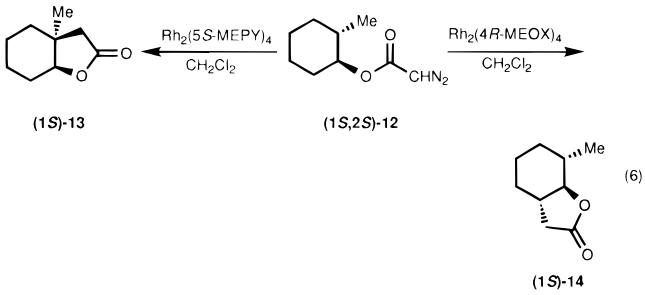
yield, %			
75	$Rh_2(5S\text{-MEPY})_4$	45 (91% ee)	49 (98% ee)
86	$Rh_2(4S\text{-MEOX})_4$	40 (99% ee)	47 (99% ee)
77	$Rh_2(4S\text{-MACIM})_4$	11 (87% ee)	66 (77% ee)

and **10** (4%).[29] Thus, this catalyst directs intramolecular C−H insertion of the (1*S*,2*R*)-enantiomer of ***rac*-6** to **(1*S*)-7** and of the (1*R*,2*S*)-enantiomer of ***rac*-6** to **(1*R*)-8** with near exclusivity. The term that we have used for this form of stereocontrol is "enantiomer differentiation".[20b] Similar results were obtained with $Rh_2(4(S)\text{-MEOX})_4$, and with $Rh_2(5(R)\text{-MEPY})_4$ or $Rh_2(4(R)\text{-MEOX})_4$ the mirror image products are formed with product distributions identical to those in eq 5. However, with $Rh_2(4(S)\text{-MACIM})_4$, like $Rh_2(4(S)\text{-MPPIM})_4$, enantiomer differentiation was not as high as with $Rh_2(5(S)\text{-MEPY})_4$ or $Rh_2(4(S)\text{-MEOX})_4$ because of a formidable match/mismatch between substrate and catalyst configurations, and relatively low stereoselectivity/regioselectivity was the outcome.

rac-trans-2-Methylcyclohexanol was resolved by the same lipase-catalyzed methodology (13 h) as was used for **6**.[22] (1*S*,2*S*)-2-Methylcyclohexanol, **(1*S*,2*S*)-11**, was isolated in 77% yield with >99% ee; **(1*R*,2*R*)-11** was recovered in 86% yield with 94.5% ee. These alcohols were converted to their corresponding diazoacetates, **(1*S*,2*S*)-12** and **(1*R*,2*R*)-12**, and their diazo decomposition was performed with a catalyst set identical to that employed for **6**. Results from catalytic decomposition of these diazoacetates are recorded in Table 2. As in reactions with **6**, a total of four products was anticipated from C−H insertion with each diazoacetate, **13**−**16**, but once



again, only two products in each set (**13** and **14**) are formed individually with specific catalysts in synthetically meaningful yields and high diastereomeric ratios and/or regioselectivities (e.g., eq 6). Exclusion of **16** from consideration because of its



(6)

simple thermal decomposition provides calculated selectivities of ≥95:5 for the formation of **13** using either $Rh_2(MEPY)_4$ or $Rh_2(MEOX)_4$ catalysts, and **14** could be formed with overall 89:11 selectivity with $Rh_2(MEOX)_4$ catalysts. With $Rh_2(MPPIM)_4$, however, preference is for the formation of **13** or **15** but with relatively low selectivity. Use of chiral dirhodium(II) caprolactamate, $Rh_2(cap)_4$,[12] under the same conditions provided **13**−**15** in low overall yield and with low selectivities; with $Rh_2(OAc)_4$ even lower yields of **13**−**15** were obtained. Reactions such as those that produce maleate and fumarate "carbene dimers", which are of major importance in reactions catalyzed by $Rh_2(cap)_4$ and $Rh_2(OAc)_4$,[2] are minimized when chiral dirhodium(II) carboxamidate catalysts are employed.

When *rac-trans*-2-methylcyclohexyl diazoacetate (***rac*-12**) was treated with the same set of catalysts as was used with

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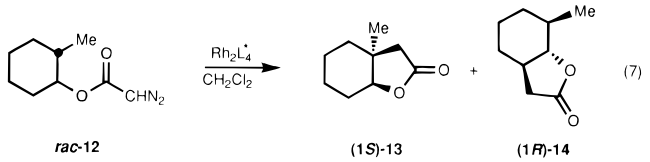
Table 2. Product Distribution from Dirhodium(II) Catalyzed Intramolecular C−H Insertion Reactions of *trans*-2-Methylcyclohexyl Diazoacetate (**12**)*a*

diazoacetate	catalyst	isolated yield, %	relative yield, %			
			13	**14**	**15**	**16**
(1*S*,2*S*)-12[c]	Rh_2(5(*S*)-MEPY)$_4$	71	92	3	2	3
	Rh_2(5(*R*)-MEPY)$_4$	64	10	74	16	t[f]
	Rh_2(4(*S*)-MEOX)$_4$	77	87	3	1	9
	Rh_2(4(*R*)-MEOX)$_4$	86	2	87	9	2
	Rh_2(4(*S*)-MPPIM)$_4$	69	58	9	7	26
	Rh_2(cap)$_4$	12	56	38	6	t
(1*R*,2*R*)-12[d]	Rh_2(5(*S*)-MEPY)$_4$	75	13	72[e]	15	t
	Rh_2(5(*R*)-MEPY)$_4$	56	88[e]	6	3	3
	Rh_2(4(*S*)-MEOX)$_4$	92	4	85[e]	9	2
	Rh_2(4(*R*)-MEOX)$_4$	74	84[e]	4	3	9
	Rh_2(4(*S*)-MPPIM)$_4$	81	3	21	76[e]	t

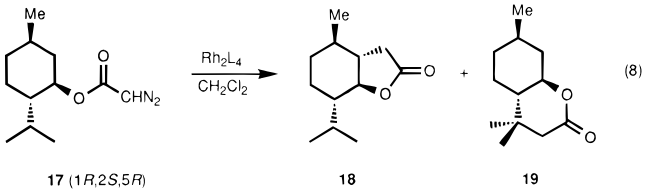
[a] Reactions were performed in refluxing CH_2Cl_2 with 1.0 mol % catalyst. [b] For C−H insertion products only. [c] >99% ee. [d] 94.5% ee. [e] ≥99% ee. [f] t = trace.

***rac*-6** in eq 5, enantiomer differentiation, predictable from the results reported in Table 2, occurred (eq 7).[29] Except for Rh_2(4(*S*)-MACIM)$_4$, for which **(1*R*)-15** was the major product (51%, 86% ee), **(1*S*)-13** and **(1*R*)-14** were preferred; *β*-lactone **16** was a minor product (≤5% with Rh_2(5(*S*)-MEPY)$_4$ and Rh_2(4(*S*)-MEOX)$_4$; 12% with Rh_2(4(*S*)-MACIM)$_4$).



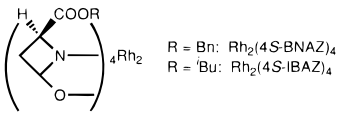
rac-12		(1*S*)-13	(1*R*)-14
yield, %			
65	Rh_2(5*S*-MEPY)$_4$	49 (80% ee)	40 (93% ee)
75	Rh_2(4*S*-MEOX)$_4$	39 (96% ee)	50 (95% ee)
56	Rh_2(4*S*-MACIM)$_4$	18 (87% ee)	19 (49% ee)

d-(+)- and *l*-(−)-Menthyl diazoacetates (MDA) have common use in intermolecular cyclopropanation reactions;[2,25,30,31] however, despite the moderate to low yields of cyclopropanation products with *d*- or *l*-MDA, there has been no mention of competitive C−H insertion reactions. Diazo decomposition of *l*-(−)-MDA (**17**) in refluxing dichloromethane produced two major isolable C−H insertion products (eq 8) with regiocontrol



17 (1*R*,2*S*,5*R*) **18** **19**

that was dependent on the catalyst employed (Table 3). The relative yields of **18** and **19** suggest the degree of match/mismatch between the carbene from *l*-(−)-MDA and catalyst configuration. With achiral Rh_2(OAc)$_4$ or Rh_2(cap)$_4$ regiocontrol was virtually absent, but chiral dirhodium(II) carboxamidates, including the [alkyl 2-oxoazetidine-4(*S*)-carboxylate]-ligated catalysts Rh_2(4(*S*)-BNAZ)$_4$ and Rh_2(4(*S*)-IBAZ)$_4$,[32] greatly influenced regioselection. The use of Rh_2(4(*S*)-MEOX)$_4$

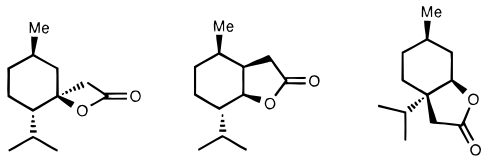


provided exclusive formation of bicyclic lactone **18**, but catalysis by Rh_2(4(*R*)-MEOX)$_4$ gave a mixture of products that included *β*-lactone **20**. Neither diastereoisomer **21** nor **22** was observed.

Table 3. Product Distribution from Dirhodium(II)-Catalyzed Intramolecular C−H Insertion Reactions of *l*-(−)-MDA (**17**) and *d*-(+)-MDA (**24**)[a]

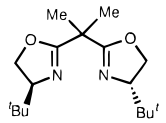
catalyst	isolated yield, %,[b] from **17** (**24**)	relative yield, %		
		18 (**25**)	**19** (**26**)	**20** (**27**)
Rh_2(OAc)$_4$	17[c]	56	44	−
Rh_2(cap)$_4$	33[d]	56	44	−
Rh_2(5(*S*)-MEPY)$_4$	85 (70)	73 (44)	27 (56)	−
Rh_2(5(*R*)-MEPY)$_4$	84 (92)	42 (75)	58 (25)	−
Rh_2(4(*S*)-MEOX)$_4$	87 (61)	>99 (29)	<1 (53)	− (18)
Rh_2(4(*R*)-MEOX)$_4$	84 (75)	28 (>99)	50 (<1)	22 (−)
Rh_2(4(*S*)-MPPIM)$_4$	72 (50)	73 (77)	27 (23)	−
Rh_2(4(*S*)-BNAZ)$_4$	63[e]	93	7	−
Rh_2(4(*S*)-IBAZ)$_4$	61[e]	95	5	−
$CuPF_6$/**23**	15 (28)[f]	93 (97)	7 (3)	−

[a] Reactions performed in refluxing CH_2Cl_2 with 1.0 mol % catalyst. [b] For C−H insertion products only. [c] Maleate and fumarate byproducts accounted for an additional 26% of reaction products. [d] Maleate and fumarate byproducts accounted for an additional 17% reaction products. [e] Maleate and fumarate byproducts amounted to an additional 22% yield for the BNAZ catalyst and 10% for the IBAZ catalyst. [f] Maleate and fumarate byproducts amounted to an additional 45−50% yield.



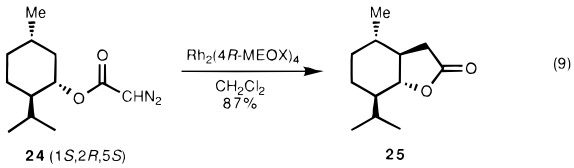
20 **21** **22**

In contrast, the copper(I) catalyst formed from $CuPF_6$ and the Evans chiral bis(oxazoline) ligand **23**[33] gave a low yield of insertion products, although with high regiocontrol, when these reactions were performed under the same conditions.



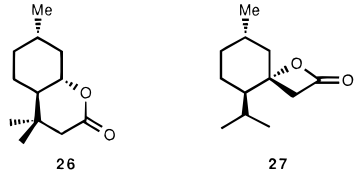
23

With *d*-(+)-menthyl diazoacetate (**24**) a mirror image of results from those obtained with *l*-(−)-MDA resulted (Table 3). Catalysis by Rh_2(4(*R*)-MEOX)$_4$ produced *γ*-lactone **25** exclusively and in high yield (eq 9). Methine C−H insertion



24 (1*S*,2*R*,5*S*) **25**

to form *δ*-lactone **26** was competitive when other catalysts were employed, and *β*-lactone **27** was observed only when diazo



26 **27**

decomposition of **24** was catalyzed by the mismatched Rh_2-

(30) Fritschi, H.; Leutenegger, U.; Siegmann, K.; Pfaltz, A.; Keller, W.; Kratky, Ch. *Helv. Chim. Acta* **1988**, *71*, 1541.
(31) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005.
(32) Doyle, M. P.; Zhou, Q.-L.; Simonsen, S. H.; Lynch, V. *Synlett* **1996**, 697.

Table 4. Product Distribution from Dirhodium(II)-Catalyzed Intramolecular C−H Insertion Reactions of (+)-Neomenthyl Diazoacetate (**28**)[a]

catalyst	isolated yield, %[b]	relative yield, % **29**	**30**	**31**
$Rh_2(OAc)_4$	16[c]	51	49	–
$Rh_2(cap)_4$	26[d]	55	45	–
$Rh_2(5(S)\text{-MEPY})_4$	65	52	45	3
$Rh_2(5(R)\text{-MEPY})_4$	75	89	11	–
$Rh_2(4(S)\text{-MEOX})_4$	77	28	39	33
$Rh_2(4(R)\text{-MEOX})_4$	97	98	2	–
CuPF6/**23**	84	94	6	t

[a] Reactions performed in refluxing CH_2Cl_2 with 1.0 mol % catalyst. [b] For C−H insertion products only. [c] Maleate and fumarate byproducts accounted for an additional 35% yield. [d] Maleate and fumarate byproducts accounted for an additional 24% yield.

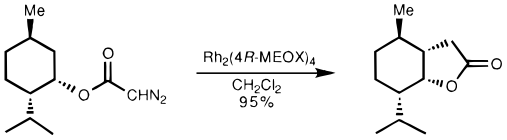
Table 5. Product Distribution from Dirhodium(II)-Catalyzed Intramolecular C−H Insertion Reactions of Nonracemic 2-Octyl Diazoacetates **32**[a]

diazoacetate	catalyst	isolated yield, %*b*	relative yield, % **33**	**34**	**35**	**36**
(*R*)-32	$Rh_2(5(S)\text{-MEPY})_4$	59	66	14	14	6
	$Rh_2(5(R)\text{-MEPY})_4$	53	43	1	14	42
	$Rh_2(4(S)\text{-MEOX})_4$	59	83	10	4	3
	$Rh_2(4(R)\text{-MEOX})_4$	71	57	2	12	29
	$Rh_2(4(S)\text{-MACIM})_4$	58	39	44	7	10
	$Rh_2(4(S)\text{-MPPIM})_4$	55	21	61	5	13
(*S*)-32	$Rh_2(5(R)\text{-MEPY})_4$	52	65	14	14	7
	$Rh_2(4(R)\text{-MEOX})_4$	53	85	9	4	2
	$Rh_2(4(S)\text{-MACIM})_4$	74	22	<1	2	76
	$Rh_2(4(S)\text{-MPPIM})_4$	72	16	<1	<1	84

[a] Reactions performed in refluxing CH_2Cl_2 with 1.0 mol % catalyst. [b] Yield obtained after distillation.

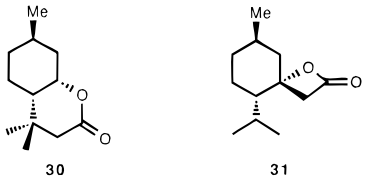
$(4(S)\text{-MEOX})_4$. Once again, with $CuPF_6$/**23** a low yield of insertion products was obtained, although with high regiocontrol, but even with *l*- and *d*-MDA this catalyst does not exhibit a match/mismatch relationship in product formation.

With the diastereomeric (+)-neomenthyl diazoacetate (**28**) regiocontrol for intramolecular C−H insertion was highest with $Rh_2(4(R)\text{-MEOX})_4$ (Table 4), but here $CuPF_6$/**23** also provided high regioselectivity and insertion product yield. The *cis*-fused γ-lactone **29** was the product of choice (eq 10), but with catalysts



28 (1*S*,2*S*,5*R*) **29** (10)

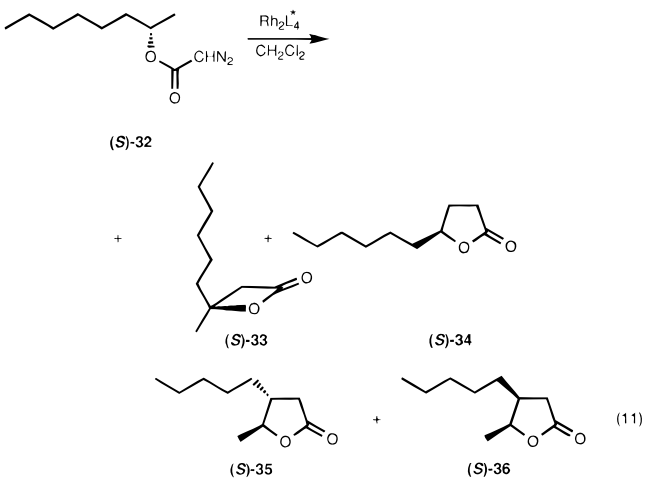
other than $Rh_2(4(R)\text{-MEOX})_4$ or $CuPF_6$/**23**, δ-lactone **30** and, to a limited extent, β-lactone **31** were also produced. In contrast



30 **31**

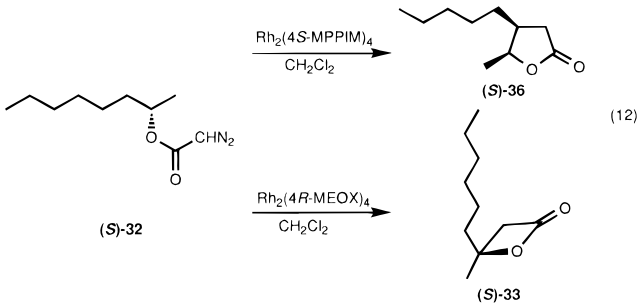
to *l*-(−)- or *d*-(+)-MDA, however, the stereochemistry of the fused lactone is *cis* (**29**) rather than *trans* (**18** and **25**).

Acyclic nonracemic 2-octyl diazoacetate showed a greater preference for β-lactone formation in reactions catalyzed by chiral dirhodium carboxamidates than did the cyclic diazoacetates that have been examined. In all, four C−H insertion products have been isolated and identified (e.g., eq 11). The



(11)

match of (*S*)-2-octyl diazoacetate with the (*R*)-series of dirhodium(II) carboxamidates and of (*R*)-2-octyl diazoacetate with the (*S*)-series of dirhodium(II) carboxamidates results (Table 5) in higher levels of regioselectivity (**33:34:35** + **36**), but the (*S*)/(*S*)- and (*R*)/(*R*)-match enhances diastereocontrol (**35**:**36**). β-Lactone **33** was formed with high regioselectivity in reactions catalyzed by $Rh_2(MEOX)_4$ (eq 12). However, with $Rh_2(4(S)\text{-}$

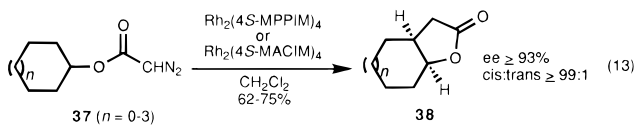


(12)

$MACIM)_4$ and, especially, $Rh_2(4(S)\text{-MPPIM})_4$ *cis*-disubstituted γ-lactone **(*S*)-36** was the principal reaction product. Curiously, the mismatch of catalyst/substrate configurations enhances **36** with $Rh_2(MEPY)_4$ and $Rh_2(MEOX)_4$ but gives the γ-lactone from normally disfavored insertion into a primary C−H bond (**34**) predominantly with the imidazolidinone series of ligated dirhodium(II) catalysts.

Discussion

In prior papers we reported that cycloalkyl diazoacetates **37** undergo highly enantioselective C−H insertion reactions with nearly complete diastereocontrol when catalyzed by $Rh_2(4(S)\text{-}$ $MPPIM)_4$ or $Rh_2(4(S)\text{-MACIM})_4$ (eq 13);[15,19] high enantiocon-

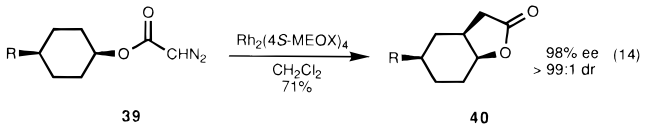


37 (*n* = 0-3) **38** (13)

trol but lower diastereocontrol (<75:25 *cis*/*trans*) characterized reactions catalyzed by $Rh_2(4(S)\text{-MEOX})_4$ and $Rh_2(5(S)\text{-MEPY})_4$. Dirhodium(II) catalysts whose ligands have the *S*-carboxylate configuration formed the bicyclic γ-lactone having the (*S*,*S*)-configuration (**38**), while the (*R*)-series of catalysts produced the enantiomers of **38**. 4-Alkylcyclohexyl diazoacetates un-

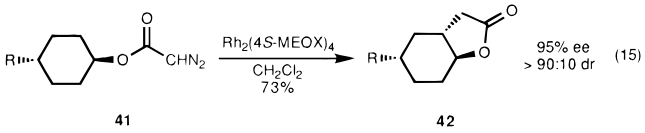
(33) Evans, D. A.; Woerpel, K. A.; Himman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726.

derwent C−H insertion with diazoacetate geometry-dependent diastereocontrol.[15a] Thus, *cis*-4-alkylcyclohexyl diazoacetate **39** (R = Me, Bu^t) gave *cis*-fused γ-lactones exclusively (eq 14),



39 **40**

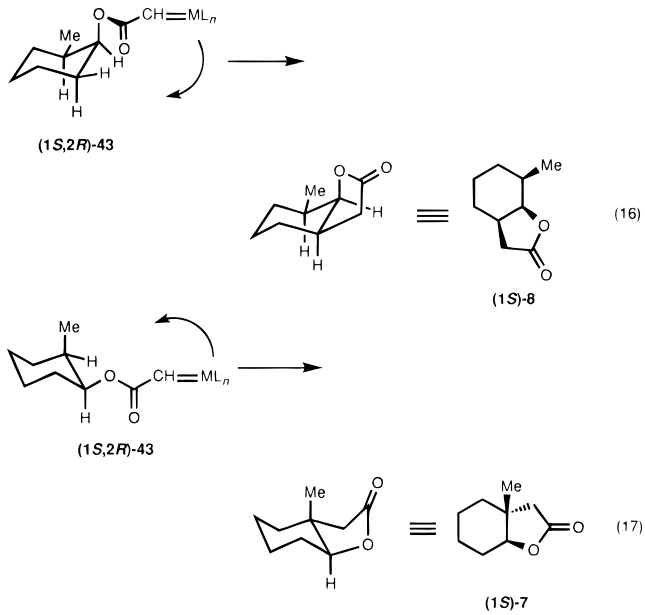
whereas *trans*-4-alkylcyclohexyl diazoacetates **41** (R = Me, Bu^t) gave *trans*-fused γ-lactones with high or exclusive diastereocontrol (eq 15). The same direction for diastereocontrol is



41 **42**

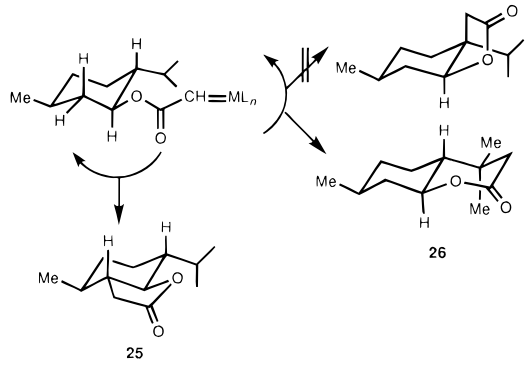
observed in catalytic diazo decomposition reactions of *cis*- and *trans*-2-methylcyclohexyl diazoacetates. The *cis*-fused lactones **8** are the exclusive products from *cis*-2-methylcyclohexyl diazoacetates **6** catalyzed by Rh_2(MPPIM)$_4$, and the *trans*-fused lactones **14** are the predominant products from Rh_2(MEOX)$_4$-catalyzed reactions of *trans*-2-methylcyclohexyl diazoacetates **12**.

The exceedingly high product diastereoselection observed in these reactions is consistent with virtually exclusive insertion into equatorial C−H bonds, as exemplified for the metal carbene derived from (**1*S*,2*R*)-6** (eqs 16 and 17). When the chiral



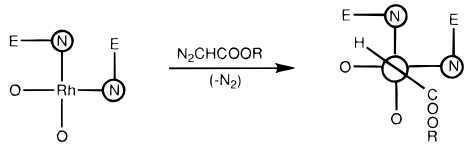
catalyst facilitates clockwise orientation for the bound carbene (e.g., Rh_2(4(*R*)-MPPIM)$_4$), insertion takes place from **(1*S*,2*R*)-43** to produce **(1*S*)-8**. When the chiral catalyst has the mirror image configuration (e.g., Rh_2(5(*S*)-MEPY)$_4$ or Rh_2(4(*S*)-MEOX)$_4$), counterclockwise orientation of the bound carbene leads to **(1*S*)-7**. Consistent with this explanation, for reactions with menthyl and neomenthyl diazoacetates the 2-isopropyl substituent is locked in the equatorial position, and access to the axial methine C−H bond at position 2 is thereby blocked (Scheme 2). Instead, as an apparent outlet for carbene reaction that takes place by clockwise orientation of the bound carbene, insertion occurs into the isopropyl methine C−H bond (**19**, **26**, or **30**). However, even with mismatched catalyst/diazoacetate

Scheme 2



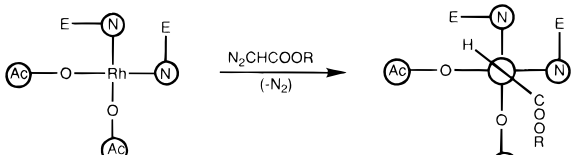
configurations, a main pathway for insertion is that which produces the γ-lactone **18**, **25**, or **29**.

The differing influence of chiral ligands of dirhodium(II) on diastereoselectivity and regioselectivity is consistent with catalyst structure. The chiral Rh_2(MEPY)$_4$ and Rh_2(MEOX)$_4$ catalysts are constructed with two closed (occupied) and two open quadrants on the dirhodium(II) face (e.g., **44**, E = COOMe). The bound carbene takes a resting position so as to minimize interactions with the ligand's ester attachments (e.g., **45**). For



44 **45**

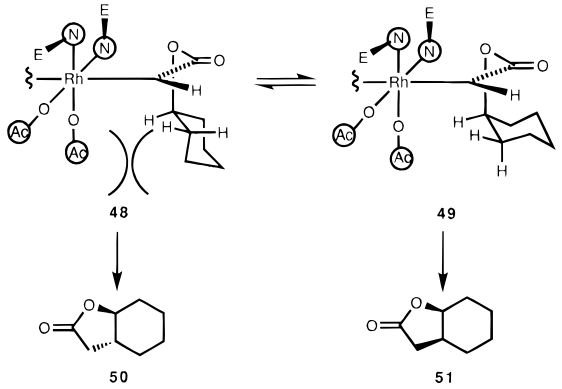
its metal carbene reactions, Rh_2(MEOX)$_4$ provides a somewhat more open framework for insertion than does Rh_2(MEPY)$_4$,[17b] and diastereocontrol is often greater for Rh_2(MEPY)$_4$ than Rh_2(MEOX)$_4$ catalysts (Tables 1 and 5), although the reverse is seen for regiocontrol (Tables 3 and 4). Selectivity differs considerably from Rh_2(MEPY)$_4$- and Rh_2(MEOX)$_4$-directed reactions with the use of chiral *N*-acylimidazolidinone-ligated dirhodium(II) catalysts. With these structures[27] the open quadrants of **44** are restricted (e.g., **46**) and the bound carbene is subject to steric influences from both the ligand's ester (E = COOMe) and acyl (Ac = NCOR) attachments (e.g., **47**).



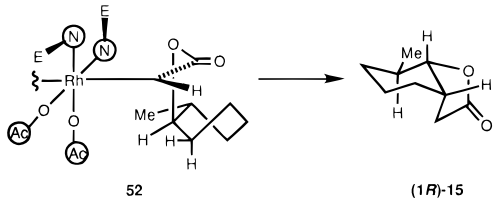
46 **47**

The influence of chiral catalyst on diastereoselection with cycloalkyl diazoacetates is understandable by reference to the conformational descriptions of metal carbene intermediates in Scheme 3. The equatorial−axial conformational equilibrium of the cyclohexyl group provides access of the carbene to equatorial C−H bonds, insertion into which yields the *trans*-fused lactone **50** or the *cis*-fused lactone **51**. (Access to axial C−H bonds is prevented by crowding of the cyclohexane ring into the catalyst face that would be required for carbene insertion.) In the absence of significant steric influences from the catalyst face adjacent to the cyclohexyl group, both diastereoisomers are produced. However, by the placement of substituents in those quadrants of the catalyst face that destabilize **48** relative to **49** (i.e., with Rh_2(4(*S*)-MACIM)$_4$ and

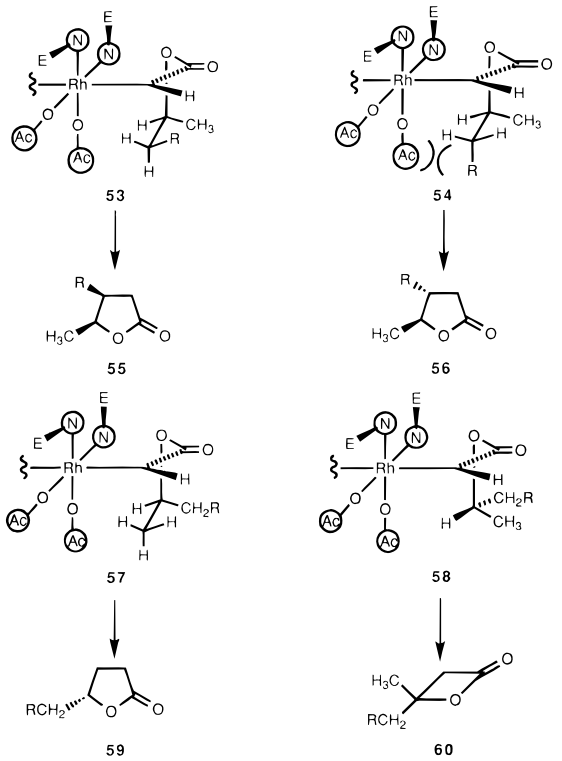
Scheme 3



Scheme 4



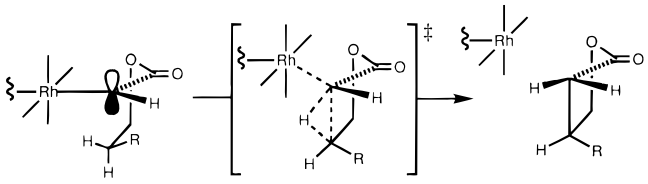
Scheme 5



Rh_2(4(*S*)-MPPIM)$_4$), diastereoselection for **51** is significantly enhanced. The unique preference shown by Rh_2(4(*S*)-MPPIM)$_4$ to convert (1*R*,2*R*)-*trans*-2-methylcyclohexyl diazoacetate, **(1*R*,2*R*)-12**, to **(1*R*)-15** may be related to steric access provided by the diaxial chair or twist conformation (Scheme 4) since a conformation like that in **48** could only provide **(1*R*)-14**.

Products from diazo decomposition of 2-octyl diazoacetates **32** are predictable from the model in Scheme 5 (R = $(CH_2)_4$-CH_3) which depicts the (*S*)-catalyst series and employs the metal carbene derived from **(*S*)-32** (for **53** and **54**) and from **(*R*)-32** (for **57** and **58**). Diastereoselectivity (**55:56**) is determined by the relative stability of **53** and **54**. Steric repulsion of R from the catalyst face in **54** accounts for the dominance of **55** over

Scheme 6



56 observed for C−H insertion from (*S*)-2-octyl diazoacetate (>84:1 for Rh_2(4(*S*)-MPPIM)$_4$ with (***S*)-32**, Table 5) and also achieved in the conversion of **3** to **4** (eq 2).[19]

The dominance of **59** in Rh_2(4(*S*)-MPPIM)$_4$-catalyzed reactions with (*R*)-2-octyl diazoacetate (and the absence of its enantiomer in reactions with (*S*)-2-octyl diazoacetate) is understandable by reference to **57**. The formation of *β*-lactone **60** through **58** can be seen as a competitive process over which ligands on dirhodium have limited control, although as seen from Table 5, the *N*-acyl group of chiral imidazolidinone-ligated dirhodium(II) catalysts does substantially inhibit this insertion process.

In the models portrayed in Schemes 3−5 for C−H insertion, reaction is initiated by overlap of the metal carbene's carbon p-orbital with the *σ*-orbital of the reacting C−H bond.[12] The formation of C−C and C−H bonds is concurrent with dissociation of the dirhodium(II) species (Scheme 6). As hydrogen migrates to the carbene center, the substituents on the carbon where insertion is taking place rotate toward the resting positions that conform to their placement in the product. Consistent with our previously reported mechanism,[12] there is no need to invoke interaction of rhodium with the migrating hydrogen,[34] nor do we have any experimental evidence for hydrogen transfer to rhodium that would result in ligand displacement or loss.[6] However, hydrogen does migrate to the site from which the rhodium complex has been released. The catalyst-dependent selectivities achieved in these reactions are compatible with the role of the dirhodium(II) carboxamidate as a template upon which carbene transformations occur.

The composite data demonstrate that chiral ligands on dirhodium(II) have a remarkable influence on diastereocontrol and regiocontrol in C−H insertion reactions of enantiomerically pure diazoacetates. Low product yields resulting, in part, from competition with intermolecular maleate and fumarate ester formation characterize reactions catalyzed by achiral dirhodium(II) catalysts, and limited data (Tables 3 and 4) suggest that a C_2-symmetric chiral bis(oxazoline) (**23**) copper(I) catalyst has similar problems with reactivity. Chiral dirhodium(II) carboxamidates not only inhibit competing reactions but also orient the attached carbene for efficient intramolecular C−H insertion. The appropriate match of catalyst and substrate configurations ensures production of single diastereoisomers/regioisomers in C−H insertion reactions.

Experimental Section

General Methods. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded from solutions in $CDCl_3$, and chemical shifts are reported in parts per million (ppm, *δ*) downfield from internal Me_4Si(TMS). Mass spectra were obtained using electron ionization at 70 eV on a quadrupole instrument. Infrared spectra were recorded by a FT-IR instrument either as a thin film on sodium chloride plates or as solutions as indicated, and absorptions are reported in wavenumbers (cm^{-1}). Elemental analyses were performed at Texas Analytical Laboratories, Inc. Dichloromethane was distilled from calcium hydride prior to use in catalytic reactions. Tetrahydrofuran was distilled from Na/benzophenone. Methanesulfonyl azide was prepared from methanesulfonyl

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chloride and sodium azide[35] and was not distilled. The preparation of Rh_2(5(*S*)-MEPY)$_4$ and Rh_2(5(*R*)-MEPY)$_4$,[24,25] Rh_2(4(*S*)-MEOX)$_4$ and Rh_2(4(*R*)-MEOX)$_4$,[17b] Rh_2(4(*S*)-MACIM)$_4$,[23] Rh_2(4(*S*)-MPPIM)$_4$ and Rh_2(4(*R*)-MPPIM)$_4$,[27] and Rh_2(4(*S*)-IBAZ)$_4$ and Rh_2(4(*S*)-BNAZ)$_4$[32] by acetate displacement from $Rh_2(OAc)_4$ has been reported in detail. *d*-(+)-Menthyl diazoacetate and *l*-(−)-menthyl diazoacetate[30] were prepared from their corresponding diazoacetoacetate esters[12] by deacylation in aqueous acetonitrile using 3.0 equiv of lithium hydroxide.

Resolution of (1*S*,2*R*)-(+)- and (1*R*,2*S*)-(−)-*cis*-2-Methylcyclohexanol was performed according to the procedure of Hult and coworkers.[22] *rac*-*cis*-2-Methylcyclohexanol (10.4 g, 91.2 mmol), *S*-ethyl thiooctanoate (17.2 g, 91.2 mmol), and 1.00 g of immobilized triacyl glycerol lipase Novozym 435 derived from *C. antartica* from Novo-Nordisk BioChem North America, Inc., were mixed with a magnetic stirrer under a slow flow of nitrogen at 39 °C for 148 h. The degree of resolution was monitored by GC using a 30 m Chiraldex G-TA column operated at 60 °C: 40.2 min for **(1*S*,2*R*)-5** and 41.6 min for **(1*R*,2*S*)-5**. At 148 h the % ee of **(1*S*,2*R*)-5** had reached >99%; the reaction mixture was then filtered, and the recovered enzyme was washed with ether. The products were separated by distillation: **(1*S*,2*R*)-5**, bp 78−80 °C (20 Torr), $[\alpha]^{20}_D = +16.2°$ (*c* 3.87, $CHCl_3$) for >99% ee (lit.[36] $[\alpha]_D = +21.8°$ [neat]), 4.24 g (37.2 mmol, 82% yield); (1*R*,2*S*)-*cis*-2-methylcyclohexyl octanoate, bp 106−108 °C (2 Torr), 6.94 g (28.9 mmol, 63% yield). Hydrolysis of the octanoate ester was performed with KOH in MeOH/H_2O (1:1) to yield **(1*R*,2*S*)-5**, bp 79−80 °C (24 Torr), $[\alpha]^{20}_D = -16.6°$ (*c* 3.83, $CHCl_3$) and $[\alpha]^{25}_D = -17.5°$ (*c* 0.16, MeOH) for 96% ee, 3.15 g (27.6 mmol, 95% yield).

***cis*-2-Methylcyclohexyl Diazoacetates 6.** ***rac*-6** was prepared in 73% overall yield from ***rac*-5** by condensation with diketene, diazo transfer from methanesulfonyl azide, and deacetylation using LiOH according to the previously described procedure:[23] yellow liquid; bp 75 °C at 0.2 Torr; ^{1}H NMR δ 5.04−5.00 (m, 1 H), 4.74 (br s, 1 H), 1.94−1.83 (m, 1 H), 1.80−1.60 (m, 2 H), 1.56−1.25 (m, 6 H), 0.89 (d, J = 6.9 Hz, 3 H); ^{13}C NMR δ 166.6, 74.5, 46.2, 34.8, 30.0, 29.4, 24.6, 21.0, 17.2; IR (film): 2121 (C═N_2), 1692 (C═O) cm^{-1}. Anal. Calcd for $C_9H_{14}N_2O_2$: C, 59.32; H, 7.74; N, 15.37. Found: C, 59.26; H, 7.78; N, 15.25. **(1*S*,2*R*)-6** was prepared in 77% overall yield from **(1*S*,2*R*)-5** according to the same procedure; bp 60−65 °C (0.06 Torr), $[\alpha]^{20}_D = +53.1$ (*c* 1.60, $CHCl_3$) for >99% ee. **(1*R*,2*S*)-6** was prepared in 73% overall yield; $[\alpha]^{20}_D = -51.7$ (*c* 1.61, $CHCl_3$) for 96% ee.

Catalytic Diazo Decomposition of *cis*-2-Methylcyclohexyl Diazoacetate. Diazoacetate **6** (0.182 g, 1.00 mmol) in 10 mL of anhydrous CH_2Cl_2 was added via syringe pump (1.0 mL/h) to a refluxing solution of the dirhodium(II) catalyst (generally 10 μmol, 1.0 mol %) in 5.0 mL of CH_2Cl_2. After refluxing for an additional hour the reaction solution was filtered through a short plug of silica gel to remove the catalyst, and the solvent was removed under reduced pressure. The residue was analyzed by NMR and GC methods and then distilled (bp 70−80 °C at 0.2 Torr). The resulting colorless liquid was separated into its individual components by radial chromatography (20:1 hexanes/EtOAc). Enantiomer separations were performed by GC with baseline resolution on a 30-m Chiraldex B-PH column operated at 100 °C for 100 min and then programmed at 0.3 °C/min to 150 °C: **(1*S*)-7**, 153 min; **(1*R*)-7**, 156 min; **(1*S*)-8**, 115 min; **(1*R*)-8**, 127 min. The enantiomer distribution of **9** was not determined, and **10** decomposed upon GC analysis to 2-methylcyclohexanone and 2-methylmethylenecyclohexane (2:3 ratio).

(1*S*,5*R*)-5-Methyl-2-oxabicyclo[4.3.0]nonan-3-one, (1*S*)-7: white solid; mp 49−51 °C; R_f = 0.31 (4:1 hexanes/EtOAc); $[\alpha]^{20}_D = -132.6°$ (*c* 0.53, $CHCl_3$) for >99% ee; ^{1}H NMR δ 3.89 (dd, J = 12.4, 3.8 Hz, 1 H), 2.29 (s, 2 H), 2.02−1.86 (comp, 2 H), 1.82−1.33 (comp, 6 H), 1.04 (s, 3 H); ^{13}C NMR δ 176.8, 86.6, 45.9, 41.1, 34.4, 24.1, 23.7, 20.6, 16.6; IR (film) 1778 cm^{-1}; mass spectrum, *m/e* (relative abundance) 154 (M, 1), 110 (12), 108 (9), 95 (13), 82 (100), 81 (14), 69 (24), 67 (49), 56 (23), 55 (26). Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.21; H, 9.16.

(1*R*,5*R*,9*R*)-9-Methyl-2-oxabicyclo[4.3.0]nonan-3-one, (1*S*)-8: colorless liquid; R_f = 0.28 (4:1 hexanes/EtOAc); $[\alpha]^{20}_D = +123.4°$ (*c* 0.71, $CHCl_3$) for >99% ee; ^{1}H NMR δ 4.36 (t, J = 3.6 Hz, 1 H), 2.67 (dd, J = 16.7, 6.5 Hz, 1 H), 2.32 (dddd, J = 11.8, 6.5, 6.2, 4.0 Hz, 1 H), 2.19 (d, J = 16.7 Hz, 1 H), 1.78−1.61 (comp, 3 H), 1.56−1.46 (m, 1 H), 1.34−1.17 (comp, 2 H), 1.15−1.00 (m, 1 H), 1.12 (d, J = 6.9 Hz, 3 H); ^{13}C NMR δ 177.6, 83.6, 38.7, 35.7, 34.0, 27.5, 27.2, 23.9, 18.5; IR (film) 1774 cm^{-1}; mass spectrum, *m/z* (relative abundance) 154 (M, 4), 126 (29), 125 (23), 111 (16), 98 (26), 97 (46), 95 (70), 94 (67), 84 (22), 82 (85), 81 (32), 68 (45), 67 (53), 56 (30), 55 (100). Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.16; H, 9.12.

(1*R*,5*S*,9*R*)-9-Methyl-2-oxabicyclo[4.3.0]nonan-3-one, (1*S*)-9, was assigned from its spectra: mass spectrum, *m/z* (relative abundance) 154 (M, 2), 126 (5), 125 (7), 111 (5), 98 (9), 97 (18), 95 (14), 94 (15), 84 (10), 82 (100), 81 (10), 68 (27), 67 (40), 56 (12), 55 (51); R_f = 0.31 (4:1 hexanes/EtOAc). The product was isolated as a 85:15 mixture with **(1*S*)-6**: ^{1}H NMR δ 3.97 (dd, J = 10.8, 4.8 Hz, 1 H), 2.56−1.18 (comp, 10 H), 1.01 (d, J = 7.0 Hz, 3 H).

(1*R*,5*R*)-5-Methyl-1-oxaspiro[5.3]nonan-2-one, (1*S*)-10: colorless liquid; R_f = 0.43 (4:1 hexanes/EtOAc); $[\alpha]^{20}_D = -7.3°$ (*c* 0.85, $CHCl_3$) for >99% ee; ^{1}H NMR δ 3.28 (d, J = 16.2 Hz, 1 H), 2.94 (d, J = 16.2 Hz, 1 H), 2.07−1.96 (m, 1 H), 1.91−1.78 (m, 1 H), 1.75−1.30 (comp, 7 H), 1.05 (d, J = 6.8 Hz, 3 H); ^{13}C NMR δ 168.7, 80.7, 45.7, 37.2, 35.1, 30.6, 23.4, 23.0, 13.8; IR (film) 1822 cm^{-1}; mass spectrum, *m/z* (relative abundance) 154 (M, 1), 112 (53), 111 (8), 110 (32), 95 (53), 84 (32), 82 (23), 81 (50), 69 (50), 68 (100), 67 (66), 56 (32), 55 (53), 53 (17). Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.95; H, 9.23.

Resolution of (1*S*,2*S*)-(+)- and (1*R*,2*R*)-(−)-*trans*-2-methylcyclohexanol was accomplished by the same procedure as that employed for the *cis*-isomer.[22] *rac*-*trans*-2-Methylcyclohexanol (9.08 g, 79.6 mmol), *S*-ethyl thiooctanoate (14.97 g, 79.6 mmol), and 1.00 g of the immobilized lipase Novozym 435 were mixed at 39 °C with a magnetic stirrer under a slow flow of nitrogen for 13 h. The degree of enzymatic resolution was monitored by GC using a 30-m Chiraldex G-PN column operated at 60 °C: 67.6 min for **(1*S*,2*S*)-11** and 70.1 min for **(1*R*,2*R*)-11**. At 13 h the % ee of **(1*S*,2*S*)-11** had reached >99% ee; the reaction mixture was then filtered, and the recovered enzyme was washed with ether. The products were separated by distillation: **(1*S*,2*S*)-11**, bp 82−84 °C (20 Torr), $[\alpha]^{20}_D = +43.9°$ (*c* 1.01, MeOH) for ≥99% ee (lit.[36] $[\alpha]_D = +42.9°$ [*c* 1, MeOH]), 3.49 g (30.6 mmol, 77% yield); (1*R*,2*R*)-*trans*-2-methylcyclohexyl octanoate, bp 89−92 °C (1 Torr), 8.59 g (35.8 mmol, 90% yield). Hydrolysis of the octanoate ester was performed with KOH in MeOH/H2O (1:1) to yield **(1*R*,2*R*)-11**, bp 82−84 °C (20 Torr), $[\alpha]^{20}_D = -42.9°$ (*c* 1.02, MeOH) for 94.5% ee (lit.[37] $[\alpha]^{25}_D = -38.2°$ [*c* 9.6, EtOH]), 3.90 g (34.2 mmol, 96% yield).

***trans*-2-Methylcyclohexyl diazoacetates 12** were prepared from the corresponding alcohols by the same procedure as employed for the synthesis of **6**: ^{1}H NMR δ 4.72 (br s, 1 H), 4.49 (dt, J = 4.5, 10.1 Hz, 1 H), 2.06−1.96 (m, 1 H), 1.80−1.00 (comp, 8 H), 0.91 (d, J = 6.5 Hz, 3 H); ^{13}C NMR δ 166.8, 79.1, 46.2, 37.5, 33.6, 32.1, 25.4, 24.8, 18.5; IR (film) 2121 (C═N_2) 1689 (C═O) cm^{-1}. Anal. Calcd for $C_9H_{14}N_2O_2$: C, 59.32; H, 7.74; N, 15.37. Found: C, 59.40; H, 7.71; N, 15.42. ***rac*-12** was prepared from ***rac*-11** as a yellow liquid in 58% overall yield; bp 75 °C (0.2 Torr). **(1*S*,2*S*)-12**: bp 60−70 °C (0.06 Torr); 72% overall yield; $[\alpha]^{20}_D = +87.6°$ (*c* 1.27, $CHCl_3$) for >99% ee. **(1*R*,2*R*)-12**: 76% overall yield; $[\alpha]^{20}_D = -84.4°$ (*c* 1.28, $CHCl_3$) for 94.5% ee.

Catalytic diazo decomposition of *trans*-2-methylcyclohexyl diazoacetate was performed by the same procedure as described for **6**. Enantiomer separations were performed by GC with baseline resolution on a 30-m Chiraldex B-PH column operated at 100 °C for 100 min and then programmed at 0.3 °C/min to 150 °C: **(1*S*)-13**, 137 min; **(1*R*)-13**, 133 min; **(1*S*)-14**, 128 min; **(1*R*)-14**, 125 min; **(1*S*)-15**, 152 min; **(1*R*)-15**, 147 min. **16** was not stable to GC analysis, decomposing to 2-methylcyclohexane and 2-methylmethylenecyclohexane.

(1*S*,6*S*)-5-Methyl-2-oxabicyclo[4.3.0]nonan-3-one, (1*S*)-13: colorless liquid; R_f = 0.25 (5:1 hexanes/EtOAc); $[\alpha]^{20}_D = -45.5°$ (*c* 1.28, $CHCl_3$) for >99% ee; ^{1}H NMR δ 4.16 (t, J = 3.8 Hz, 1 H), 2.32 (s, 2 H), 2.03−1.92 (m, 1 H), 1.76−1.32 (comp, 7 H), 1.17 (s, 3 H); ^{13}C

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NMR δ 176.7, 84.0, 45.0, 38.2, 33.0, 25.5, 21.9, 20.8, 19.8; IR (film) 1783 cm^{-1}; mass spectrum, *m/z* (relative abundance) 154 (M, 6), 108 (11), 95 (18), 93 (16), 82 (100), 81 (17), 70 (14), 69 (23), 68 (13), 67 (34), 56 (21), 55 (28). Anal. Calcd for C9H14O2: C, 70.10; H, 9.15. Found: C, 70.16; H, 9.12.

(1*R*,5*S*,9*S*)-9-Methyl-2-oxabicyclo[4.3.0]nonan-3-one, (1*S*)-14: colorless liquid; R_f = 0.29 (5:1 hexanes/EtOAc); $[\alpha]^{20}_D$ = +134.5° (*c* 0.40, $CHCl_3$) for >99% ee; ^{1}H NMR δ 3.44 (t, *J* = 10.4 Hz, 1 H), 2.52 (dd, *J* = 16.1, 6.2 Hz, 1 H), 2.23 (dd, *J* = 16.1, 13.0 Hz, 1 H), 2.05−1.69 (comp, 5 H), 1.47−1.00 (comp, 3 H), 1.06 (d, *J* = 6.2 Hz, 3 H); ^{13}C NMR δ 176.6, 90.7, 44.2, 36.7, 36.1, 33.3, 28.2, 25.3, 18.5; IR (film) 1788 cm^{-1}; mass spectrum, *m/z* (relative abundance) 154 (M, 1), 97 (13), 95 (13), 82 (100), 81 (20), 68 (26), 67 (39), 55 (43), 54 (29). Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.18; H, 9.21.

(1*R*,5*R*,9*S*)-9-Methyl-2-oxabicyclo[4.3.0]nonan-3-one, (1*S*)-15: colorless liquid; R_f = 0.24 (5:1 hexanes/EtOAc); $[\alpha]^{20}_D$ = −33.5° (*c* 0.71, $CHCl_3$); ^{1}H NMR δ 4.09 (dd, *J* = 7.6, 6.5 Hz, 1 H), 2.72−2.60 (m, 1 H), 2.43 (d, *J* = 16.6 Hz, 1 H), 2.36 (dd, *J* = 16.6, 1.8 Hz, 1 H), 1.74−1.34 (comp, 7 H), 1.05 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR δ 177.2, 85.2, 34.2, 33.4, 33.3, 29.7, 25.9, 19.4, 18.4; IR (film) 1788 cm^{-1}; mass spectrum, *m/z* (relative abundance) 154 (M, 5), 126 (32), 98 (26), 97 (47), 95 (46), 94 (64), 82 (78), 68 (42), 67 (42), 56 (24), 55 (100). Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.04; H, 9.06.

(1*R*,5*S*)-5-Methyl-1-oxaspiro[5.3]nonan-2-one, (1*S*)-16: colorless liquid; R_f = 0.32 (5:1 hexanes/EtOAc); ^{1}H NMR δ 3.19 (d, *J* = 16.2 Hz, 1 H), 2.88 (d, *J* = 16.2 Hz, 1 H), 2.05−1.76 (comp, 5 H), 1.69−1.55 (m, 1 H), 1.42−1.25 (comp, 2 H), 1.16−1.05 (m, 1 H), 1.01 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR δ 168.6, 81.5, 42.1, 37.7, 35.9, 31.6, 24.0, 23.6, 14.2; IR (film) 1821 cm^{-1}; mass spectrum, *m/z* (relative abundance) 154 (M, not observed), 112 (61), 110 (32), 95 (48), 84 (36), 82 (22), 81 (46), 69 (50), 68 (100), 67 (64), 56 (35), 55 (57), 54 (15), 53 (20).

Catalytic diazo decomposition of *l*-(−)- and *d*-(+)-menthyl diazoacetates was performed by the same procedure as described for **6** except that the catalyst was dissolved in 10−12 mL of anhydrous CH_2Cl_2. Diastereoisomer and regioisomer separations were performed by GC with baseline resolution on a 30-m methyl phenyl silicone column. Spirolactones **20** and **27** were not stable to GC analysis. Reaction products were isolated by column chromatography on silica gel (5:1 hexanes/ethyl acetate); the order of elution was β-lactone, γ-lactone, and δ-lactone.

(1*R*,5*R*,6*R*,9*S*)-9-Isopropyl-6-methyl-2-oxabicyclo[4.3.0]nonan-3-one, 18: white solid; mp 67−69 °C; $[\alpha]^{22}_D$ = +132.8° (*c* 1.05, $CHCl_3$); ^{1}H NMR δ 3.70 (t, *J* = 10.5 Hz, 1 H), 2.54 (dd, *J* = 16.2, 6.4 Hz, 1 H), 2.18 (dd, *J* = 16.2, 13.2 Hz, 1 H), 1.99−1.88 (m, 1 H), 1.82−1.56 (comp, 4 H), 1.53−1.38 (m, 1 H), 1.26−0.98 (comp, 2 H), 0.94 (d, *J* = 6.8 Hz, 6 H), 0.89 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR δ 176.7, 86.3, 51.2, 46.7, 35.0, 34.6, 34.4, 28.5, 25.0, 19.8, 19.7, 17.8; IR ($CHCl_3$) 1769 cm^{-1}. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.29; H, 10.34.

(1*S*,6*R*,9*S*)-5,5,9-Trimethyl-2-oxabicyclo[4.4.0]decan-3-one, 26: white solid; mp 40−42 °C; $[\alpha]^{22}_D$ = −10.6° (*c* 0.96, $CHCl_3$); ^{1}H NMR δ 4.07 (dt, *J* = 4.2, 11.0, 1 H), 2.42 (d, *J* = 17.1 Hz, 1 H), 2.28 (d, *J* = 17.1 Hz, 1 H), 2.14 (dtd, *J* = 12.2, 3.8, 2.0 Hz, 1 H), 1.85 (dq, *J* = 12.4, 3.1 Hz, 1 H), 1.79−1.72 (m, 1 H), 1.60−1.44 (m, 1 H), 1.33−0.89 (comp, 4 H), 0.99 (s, 3 H), 0.97 (d, *J* = 6.6 Hz, 3 H), 0.95 (s, 3 H); ^{13}C NMR δ 171.3, 79.7, 48.2, 46.2, 41.2, 34.2, 31.8, 31.3, 28.4, 23.9, 21.9, 21.7; IR ($CHCl_3$) 1721 cm^{-1}. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.36; H, 10.25.

5-Isopropyl-8-methyl-1-oxaspiro[5.3]nonan-2-ones 20 and 27 from reactions of **17** with Rh_2(4(*R*)-MEOX)$_4$ or of **24** with Rh_2(4(*S*)-MEOX)$_4$ underwent decomposition in attempted chromatographic purifications. Their presence, however, was confirmed in reaction mixtures by characteristic ^{1}H NMR absorptions at δ 3.33 (dd, *J* = 16.3, 1.4 Hz, 1 H) and 2.91 (d, *J* = 16.3 Hz, 1 H). The carbonyl absorption in the IR at 1814 cm^{-1} confirmed the β-lactone ring.

(1*S*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl Diazoacetate, 28. Diketene (1.1 mL, 0.019 mol) was added over 10 min to an ice bath-cooled solution of (+)-neomenthol (2.61 g, 0.0167 mol) and triethylamine (0.22 mL, 1.6 mmol) in 25 mL of anhydrous THF. The resulting light brown-orange-colored solution was stirred at room temperature for 24 h, after which methanesulfonyl azide (2.32 g, 0.0192 mol) and triethylamine (2.67 mL, 0.0192 mol) were added, and stirring was continued overnight. A solution of lithium hydroxide (1.38 g, 0.0576 mol) in 20 mL of water was then added, and the dark brown solution was stirred for an additional 6 h. The aqueous THF solution was extracted three times with 50-mL portions of ether, and the combined ether solution was washed three times with 50-mL portions of water and brine before drying over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (10:1 hexanes/ethyl acetate) to provide 2.70 g of a yellow oil identified as **28** (75% yield): $[\alpha]^{22}_D$ = + 26.6 (*c* 1.04, $CHCl_3$); ^{1}H NMR δ 5.28 (br s, 1 H), 4.72 (br s, 1 H), 1.97 (dq, *J* = 14.4, 3.2Hz, 1 H), 1.80−1.22 (comp, 5 H), 1.12−0.90 (comp, 3 H), 0.89 (d, *J* = 5.9 Hz, 6 H), 0.86 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR δ 165.9, 71.7, 46.8, 46.1, 39.3, 34.7, 29.2, 26.4, 24.9, 22.1, 20.8, 20.7; IR ($CHCl_3$) 2113 (C═N_2), 1685 (C═O) cm^{-1}. Anal. Calcd for $C_{12}H_{20}N_2O_2$: C, 64.26; H, 8.98; N, 12.49. Found: C, 64.17; H, 9.09; N, 12.93.

Catalytic diazo decomposition of (+)-neomenthyl diazoacetate (28) was performed by the same procedure as described for **6**. Diastereoisomer and regioisomer separations were performed by GC with baseline resolution on a 30-m methyl phenyl silicone column. Spirolactone **31** was not stable to GC analysis.

(1*S*,5*R*,6*R*,9*S*)-9-Isopropyl-6-methyl-2-oxabicyclo[4.3.0]nonan-3-one, 29: colorless liquid; $[\alpha]^{22}_D$ = +44.0° (*c* 1.02, $CHCl_3$); ^{1}H NMR δ 4.57 (t, *J* = 3.7 Hz, 1 H), 2.62 (dd, *J* = 16.8, 6.6 Hz, 1 H), 2.35 (d, *J* = 16.8 Hz, 1 H), 1.86−1.68 (comp, 4 H), 1.28−1.08 (comp, 3 H), 0.94−0.85 (m, 1 H), 0.99 (d, *J* = 6.7 Hz, 3 H), 0.95 (d, *J* = 6.7 Hz, 3 H), 0.93 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR δ 177.8, 81.1, 45.8, 43.6, 36.8, 33.0, 32.0, 29.7, 23.8, 21.0, 20.6, 20.0; IR ($CHCl_3$) 1767 cm^{-1}. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.51; H, 10.35.

(1*S*,6*S*,9*R*)-5,5,9-Trimethyl-2-oxabicyclo[4.4.0]decan-3-one, 30: colorless liquid; $[\alpha]^{22}_D$ = −48.6° (*c* 1.10, $CHCl_3$); ^{1}H NMR δ 4.72 (q, *J* = 2.5 Hz, 1 H), 2.33 (d, *J* = 18.1 Hz, 1 H), 2.24 (d, *J* = 18.1 Hz, 1 H), 2.09 (dq, *J* = 14.4, 3.3 Hz, 1 H), 1.81−1.59 (comp, 3 H), 1.37−1.09 (comp, 3 H), 0.98−0.90 (m, 1 H), 1.12 (s, 3 H), 0.99 (s, 3 H), 0.88 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR δ 172.3, 76.1, 43.0, 40.6, 39.4, 33.8, 32.3, 29.3, 27.2, 25.6, 22.0, 21.8; IR ($CHCl_3$) 1717 cm^{-1}. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.30; H, 10.38.

(1*S*,5*S*,8*R*)-5-Isopropyl-8-methyl-1-oxaspiro[5.3]nonan-2-one, 31: colorless liquid; $[\alpha]^{22}_D$ = −4.56° (*c* 1.03, $CHCl_3$); ^{1}H NMR δ 3.52 (d, *J* = 16.4 Hz, 1 H), 2.87 (d, *J* = 16.4 Hz, 1 H), 2.17−1.36 (comp, 9 H), 0.98 (d, *J* = 6.8 Hz, 3 H), 0.92 (d, *J* = 6.8 Hz, 3 H), 0.90 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR 168.6, 81.7, 47.0, 46.8, 44.9, 34.3, 29.1, 26.2, 23.4, 21.8, 21.6, 18.3; IR ($CHCl_3$) 1813 cm^{-1}. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.36; H, 10.35.

2-Octyl Diazoacetates 32. To a solution of (*R*)-2-octanol (4.59 g, 35.3 mmol) and triethylamine (0.18 g, 1.8 mmol) in 50 mL of dry THF cooled at 0 °C was added diketene (4.45 g, 53.0 mmol) over 30 min. The resulting solution was stirred for 1 h at 0 °C and then for 12 h at room temperature, after which the solvent was evaporated under reduced pressure, and the crude product was diluted with ether (100 mL), passed through a short plug of silica gel, and then distilled under reduced pressure (bp 116−119 °C at 0.6 Torr) to afford 7.28 g of a colorless liquid identified as 2-octyl acetoacetate (50.9 mmol, 96% yield): ^{1}H NMR δ 4.96 (sex, *J* = 6.2 Hz, 1 H), 3.43 (s, 2 H), 2.27 (s, 3 H), 1.70−1.53 (m, 1 H), 1.52−1.42 (m, 1 H), 1.40−1.20 (m, 8 H), 1.24 (d, *J* = 6.2 Hz, 3 H), 0.88 (t, *J* = 6.4 Hz, 3 H); enol form at 5.02 (s, 1 H). 1.94 (s, 3 H); ^{13}C NMR δ 200.7, 166.8, 72.4, 50.5, 35.8, 31.7, 30.1, 29.1, 25.3, 22.6, 19.8, 14.0.

To a solution of the acetoacetate ester (3.58 g, 16.7 mmol) in dry acetonitrile (30 mL) were added triethylamine (1.69 g, 16.7 mmol) and then methanesulfonyl azide (2.43 g, 20.1 mmol). The resulting solution was stirred for 4 h at room temperature, and then $LiOH·H_2O$ (2.11 g, 50.2 mmol) in 43 mL of H_2O (5% in H_2O) was added. This mixture was stirred for 5 h and then diluted with H_2O (200 mL) and extracted three times with 50-mL portions of ether. The combined ether extract was washed twice with 150-mL portions of water and once with 150 mL of brine and then dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The crude diazo ester was passed

through a short plug of silica gel (EtOAc:hexanes = 1:1) and then distilled (bp 70−75 °C at 0.3 Torr) to yield 2.29 of a yellow liquid identified as (*R*)-2-octyl diazoacetate (11.5 mmol, 69% yield): $[\alpha]^{22}_D$ = −27.8° (*c* 1.45, $CHCl_3$); ^{1}H NMR δ 4.98 (sex, *J* = 6.1 Hz, 1 H), 4.71 (s, 1 H), 1.67−1.40 (comp, 2 H), 1.40−1.20 (comp, 8 H), 1.23 (d, *J*= 6.1 Hz, 3 H), 0.88 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR δ 166.7, 71.9, 46.3, 36.1, 31.8, 29.2, 25.4, 22.6, 20.2, 14.1; IR (film): 2116 (C=N_2), 1695 (C=O) cm^{-1}. Anal. Calcd for $C_{10}H_{18}N_2O_2$: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.68; H, 9.46; N, 14.01. ***rac*-32** and **(*S*)-32** were prepared by the same procedure in 64% and 71% overall yield, respectively; for **(*S*)-32**, $[\alpha]^{20}_D$ = +27.7° (*c* 1.44, $CHCl_3$).

Catalytic Diazo Decomposition of 2-Octyl Diazoacetates (32). The diazo compound (0.198 g, 1.00 mmol) in 10 mL of anhydrous CH_2Cl_2 was added via syringe pump (1.0 mL/h) to a refluxing solution of dirhodium(II) catalyst (10 μmol, 1.0 mol %) in 20 mL of CH_2Cl_2. After refluxing for an additional hour, the reaction solution was filtered through a short plug of silica gel, and the solvent was removed under reduced pressure. The residue was analyzed by NMR and GC methods and then distilled (bp 80-85 °C at 0.2 Torr). The resulting colorless liquid was separated into its individual components by column chromatography on silica gel (9:1 hexanes/EtOAc) with elution in the order **33**, **35**, and **36**. γ-Decanolactone **34** was identified by comparison with an authentic sample. Enantiomer separations were performed by GC with baseline resolution on 30-m Chiraldex B-PH (**33** and **35**) and G-TA (**34** and **36**) columns operated at 80 °C for 80 min and then programmed at 0.5 °C/min to 150 °C: **33**, 147.3 min ((***R*)-33**) and 148.9 min ((***S*)-33**); **35**, 177.7 min ((**4*R*,5*S*)-35**) and 180.1 min ((**4*S*,5*R*)-35**); **36**, 207.5 min ((**4*R*,5*R*)-36)** and 210.8 min ((**4*S*,5*S*)-36**); **34**, 193.9 min ((***S*)-34**) and 196.8 min ((***R*)-34**).

4-Methyl-4-(*n*-hexyl)-1-oxacyclobutan-2-one (33): $[\alpha]^{21}_D$ = +4.8° (*c* 1.17, $CHCl_3$) from (***R*)-32** with Rh_2(5(*R*)-MEPY)$_4$; ^{1}H NMR δ 3.19 (d, *J* = 16.1 Hz, 1 H), 3.10 (d, *J* = 16.1 Hz, 1 H), 1.92−1.74 (comp, 2 H), 1.57 (s, 3 H), 1.45−1.24 (comp, 8 H), 0.90 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR δ 168.3, 78.8, 47.5, 39.5, 31.7, 29.3, 24.3$_4$, 24.2$_7$, 22.6, 14.1; IR ($CHCl_3$): 1814 (C=O) cm^{-1}; mass spectrum, *m/z* (relative abundance) 126 (M − CO_2, 7), 113 (7), 110 (7), 100 (67), 85 (30), 69 (43), 58 (57), 57 (42), 56 (100), 55 (66). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.65. Found: C, 70.43; H, 10.61.

trans*-Dihydro-5-methyl-4-(*n*-pentyl)-2(3*H*)-furanone (35):** $[\alpha]^{21}_D$ = +66.6° (*c* 0.35, $CHCl_3$) from (R*)-32** with Rh_2(5(*R*)-MEPY)$_4$; ^{1}H NMR δ 4.21 (dq, *J* = 7.6, 6.2 Hz, 1 H), 2.68 (dd, *J* = 17.3, 8.2 Hz, 1 H), 2.21 (dd, *J* = 17.3, 9.6 Hz, 1 H), 2.13−1.99 (m, 1 H), 1.58−1.50 (m, 1 H), 1.40 (d, *J* = 6.2 Hz, 3 H), 1.39−1.24 (comp, 7 H), 0.90 (t, *J* = 6.6 Hz, 3 H); stereochemical assignment consistent with analogous *trans*-disubstituted γ-lactones;[38−40] ^{13}C NMR δ 176.6, 82.3, 43.5, 35.6, 32.6, 31.8, 27.4, 22.6, 20.0, 14.1; IR ($CHCl_3$): 1770 cm^{-1}; mass spectrum, *m/z* (relative abundance) 155 (M − 15, 3), 128 (5), 109 (6), 98 (64), 95 (14), 83 (12), 70 (85), 69 (46), 57 (27), 56 (100), 55 (86). Anal. (**35** + **36**) Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.65. Found: C, 70.48; H, 10.69.

cis*-Dihydro-5-methyl-4-(*n*-pentyl)-2(3*H*)-furanone (36):** $[\alpha]^{21}_D$ = +2.5° (*c* 0.52, $CHCl_3$) from (R*)-32** with Rh_2(5(*R*)-MEPY)$_4$; ^{1}H NMR δ 4.70 (quin, *J* = 6.6 Hz, 1 H), 2.56 (dd, *J* = 14.8, 7.8 Hz, 2 H), 2.56−2.48 (m, 1 H), 2.24 (dd, *J* = 14.8, 8.2 Hz, 1 H), 1.52−1.40 (m, 1 H), 1.39−1.23 (m, 7 H), 1.27 (d, *J* = 6.6 Hz, 3 H), 0.90 (t, *J* = 6.7 Hz, 2 H); stereochemical assignment consistent with analogous *cis*-disubstituted γ-lactones;[38−40] ^{13}C NMR δ 176.9, 79.5, 39.0, 33.9, 31.9, 28.7, 27.5, 22.6, 15.5, 14.1; IR ($CHCl_3$): 1773 cm^{-1}; mass spectrum, *m/z* (relative abundance) 170 (M, 1), 128 (7), 109 (6), 98 (70), 95 (12), 83 (14), 70 (86), 69 (43), 57 (30), 56 (100), 55 (86).

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