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ENHANCEMENT OF ENANTIOCONTROL/DIASTEREOCONTROL IN CATALYTIC INTRAMOLECULAR CYCLOPROPANATION AND CARBON-HYDROGEN INSERTION REACTIONS OF DIAZOACETATES WITH Rh_2(4*S*-MPPIM)$_4$

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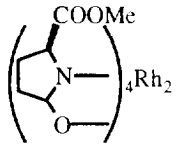
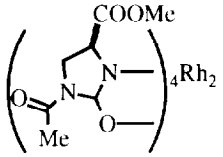
Summary: *Dirhodium(II) tetrakis[methyl 1-(3-phenylpropanoyl)imidazolidin-2-one-4(S)-carboxylate], Rh_2(4S-MPPIM)$_4$, provides significant enhancement in enantiocontrol for intramolecular cyclopropanation reactions of allylic diazoacetates and optimal enantiocontrol/diastereocontrol for intramolecular C-H insertion reactions of secondary alkyl diazoacetates.*

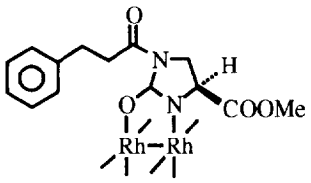
Enantiocontrol in intramolecular cyclopropanation and carbon-hydrogen insertion reactions of diazoacetate esters catalyzed by dirhodium(II) tetrakis[methyl 2-oxapyrrolidine-5(*R* or *S*)-carboxylate], Rh_2(5*R*-MEPY)$_4$ or Rh_2(5*S*-MEPY)$_4$, has generally been exceptional.[1-11] Cyclopropane products derived from allylic diazoacetates[6] and γ-lactones from secondary alkyl diazoacetates[8-10] have been formed in high yield with enantioselectivities ≥ 94% ee. However, there are notable exceptions. With 3-alkyl/aryl-2(*E*)-alken-1-yl diazoacetates, Rh_2(MEPY)$_4$ catalyzed intramolecular cyclopropanations occur with lower ee's (< 85%), and 2-methallyl diazoacetate forms the corresponding cyclopropane product with only 7% ee.[6] Secondary alkyl diazoacetates undergo intramolecular C-H insertion catalyzed by Rh_2(MEPY)$_4$ with high enantiocontrol, but diastereocontrol is often low.[8,9] The use of dirhodium(II) tetrakis-[methyl 1-acetylimidazolidin-2-one-4(*S*)-carboxylate], Rh_2(4*S*-MACIM)$_4$, has been demonstrated to improve diastereocontrol (up to 99:1 cis:trans), but enantiocontrol in selected cases is limited; for example, < 90% ee with cyclopentyl diazoacetates.[8] We now report the use of a new imidazolidinone ligated dirhodium(II) catalyst that provides dramatic improvement in enantiocontrol and diastereocontrol for intramolecular cyclopropanation and C-H insertion reactions.



Rh_2(5*S*-MEPY)$_4$



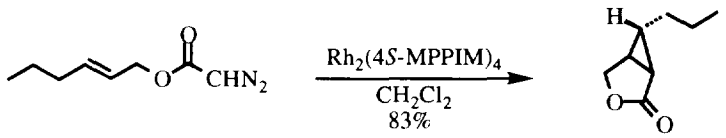
Rh_2(4*S*-MACIM)$_4$



Rh_2(4*S*-MPPIM)$_4$

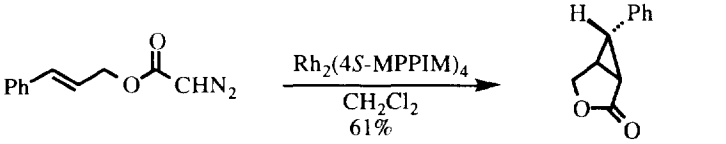
Dirhodium(II) tetrakis[methyl 1-(3-phenylpropanoyl)imidazolidin-2-one-4(*S*)-carboxylate], Rh_2(4*S*-MPPIM)$_4$, was prepared by acetate displacement from rhodium(II) acetate, and the imidazolidinone-carboxylate was synthesized from L-asparagine by a procedure identical to that reported for the ligand of Rh_2(4*S*-MACIM)$_4$.[6] The *N*-3-phenylpropanoyl attachment was selected to achieve distal control over the approach of the reacting bond to the carbene center. As with previously prepared chiral dirhodium(II) carboxamidate catalysts,[1,11] Rh_2(4*S*-MPPIM)$_4$ has two oxygen and two nitrogen donor atoms bound to each rhodium, and each pair of donor atoms is oriented in a cis (*cis*-2,2) configuration.[12]

For 2(*E*)-hexen-1-yl diazoacetate (**1**), catalysis by Rh_2(4*S*-MPPIM)$_4$ (1.0 mol %) produced the intramolecular cyclopropanation product, [1*R*-(1α,5α,6β)]-6-*n*-propyl-3-oxabicyclo[3.1.0]hexan-2-one (**2**) in 95% ee compared to 85% ee with Rh_2(5*S*-MEPY)$_4$ and 87% ee with Rh_2(4*S*-MACIM)$_4$ (eq. 1).[6] Similarly, *trans*-3-phenyl-2-propen-1-yl



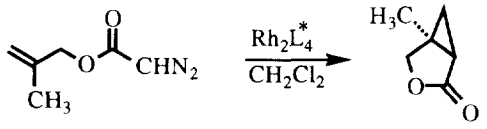
1 **2**, 95% ee (1)

diazoacetate (**3**) yielded **4** in 96% ee with Rh_2(4*S*-MPPIM)$_4$ as the catalyst compared to 80% ee with Rh_2(4*S*-MACIM)$_4$ and 68% ee with Rh_2(5*S*-MEPY)$_4$ (eq. 2).[13] However, the advantage of Rh_2(4*S*-MPPIM)$_4$ is most



3 **4**, 96% ee (2)

evident in the results from intramolecular cyclopropanation of 2-methallyl diazoacetate (eq. 3). A catalyst initially



5 **6**

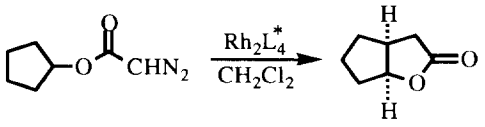
	yield, %	*ee, %*
Rh_2(4*S*-MPPIM)$_4$	75	89
Rh_2(4*S*-MCHIM)$_4$	72	83
Rh_2(4*S*-MACIM)$_4$	90	78
Rh_2(5*S*-MEPY)$_4$	72	7

(3)

perceived to be more sterically constrained than Rh_2(4*S*-MPPIM)$_4$, dirhodium(II) tetrakis[methyl 1-(cyclohexylacetyl)-imidazolidin-2-one-4(*S*)-carboxylate], Rh_2(4*S*-MCHIM)$_4$,[12] gave **6** in 83% ee; however, **2** was produced in 94% ee (64% yield) with the use of this catalyst. Neither Rh_2(4*S*-MPPIM)$_4$ nor Rh_2(4*S*-MCHIM)4 provided any advantage in % ee over Rh_2(5*S*-MEPY)$_4$ for intramolecular cyclopropanation of the homoallylic 3-methyl-3-buten-1-yl diazoacetate (78 and 74% ee, respectively, relative to 83% ee).[6] Reactions were performed in refluxing CH_2Cl_2 with controlled addition of the diazoacetate: to a refluxing solution of the catalyst (1.0 mol %) in 20 mL of anhydrous CH_2Cl_2 was

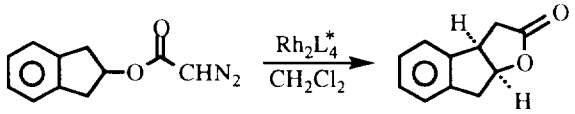
added the diazo compound (1.0 mmol) in 5 mL of CH_2Cl_2 over 10-12 h; yields are those of the pure product obtained from distillation. Values for % ee were determined as previously described.[6]

Among secondary alkyl diazoacetates,[8-11] cyclopentyl diazoacetate stands out as providing the lowest level of enantiocontrol in C-H insertion reactions of secondary cycloalkyl diazoacetates with, optimally, 89% ee from Rh_2(4*S*-MACIM)$_4$ catalysis.[8] Use of Rh_2(4*S*-MPPIM)$_4$ increases enantioselectivity to 92% ee (eq. 4). With 2-indanyl diazoacetate (**9**) enhancement of enantioselectivity is even more pronounced, leading to **10** in 75% yield with 92% ee.[14]



7 **8**

	yield, %	*ee, %*	
Rh_2(4*S*-MPPIM)$_4$	67	93	(4)
Rh_2(4*S*-MACIM)$_4$	40	89	
Rh_2(5*S*-MEPY)$_4$	54	40	

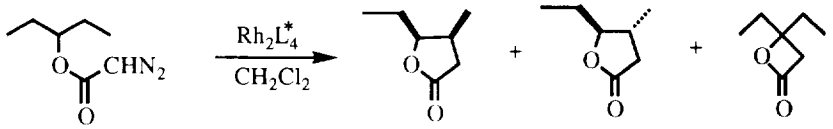


9 **10**

Rh_2(4*S*-MPPIM)$_4$	75	92	(5)
Rh_2(4*S*-MACIM)$_4$	20	79	
Rh_2(5*S*-MEPY)$_4$	35	36	

In the case of cyclohexyl diazoacetate, enantioselectivity is only slightly enhanced (to 98% ee with Rh_2(4*S*-MPPIM)$_4$ from 97% ee with Rh_2(4*S*-MACIM)$_4$: cis isomer) but diastereocontrol is diminished (to 96:4 cis:trans from 99:1).[15]

Enantioselectivity, diastereoselectivity, and regioselectivity become important considerations in catalytic C-H insertion reactions of 3-pentyl diazoacetate. Three products are formed (eq. 6),[14] and their respective distributions as a function of catalyst are reported in Table 1. Diastereocontrol and regiocontrol are optimal with the imidazolidinone-ligated dirhodium(II) catalysts, whereas overall enantiocontrol for **12** and **13** is highest with Rh_2(4*S*-MEOX)$_4$. However, only with Rh_2(4*S*-MPPIM)$_4$ is the full compliment of selectivities successfully achieved. Furthermore, this result suggests



11 **12** **13** **14** (6)

Table 1. Selectivity in Catalytic C-H Insertion Reactions of 3-Pentyl Diazoacetate

catalyst	isolated yield, %	relative yield, %			% ee	% ee
		12	**13**	**14**	**12**	**13**
Rh_2(4*S*-MCHIM)$_4$	90	95	2	3	99	-
Rh_2(4*S*-MPPIM)$_4$	85	92	3	5	99	-
Rh_2(4*S*-MACIM)$_4$	83	92	5	3	86	36
Rh_2(5*S*-MEPY)$_4$	75	73	20	7	98	71
Rh_2(4*S*-MEOX)$_4$	86	60	27	13	98	92

that the high levels of diastereoselectivity and enantioselectivity that characterize C-H insertion reactions of secondary cycloalkyl diazoacetates[8] can now be extended to acyclic secondary alkyl diazoacetates.

The dramatic improvements in % ee and, in some cases, product yield with the use of Rh_2(4*S*-MPPIM)$_4$ or Rh_2(4*S*-MCHIM)$_4$ are presumably due to a tighter orientation of the reacting carbene by the two pendant *N*-alkyl substituents of the catalyst which are across the rhodium face from (distal to) the sites of carboxylate attachment.[6] Efforts are underway to further elaborate this advantage.

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12. Configuration consistent with ^{1}H and ^{13}C NMR spectra of the catalyst and confirmed by an X-ray structure of its bis-acetonitrile complex.
13. The *N*-phenylacetyl analog of Rh_2(4*S*-MPPIM)$_4$ produced **2** in 90% ee and **4** in 86% ee.[6]
14. Spectral and elemental analyses are consistent with the reported structures. The % ee values were determined by GC with baseline separation on a Chiraldex G-TA column (**8** and **10**) or a B-PH column (**12** and **13**).
15. Similar selectivities (97:3 cis:trans, 98% ee for cis-isomer) were observed with Rh_2(4*S*-MCHIM)$_4$.

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