Enantiocontrol in intramolecular cyclopropanation of diazoketones. Conformational control of metal carbene alignment*

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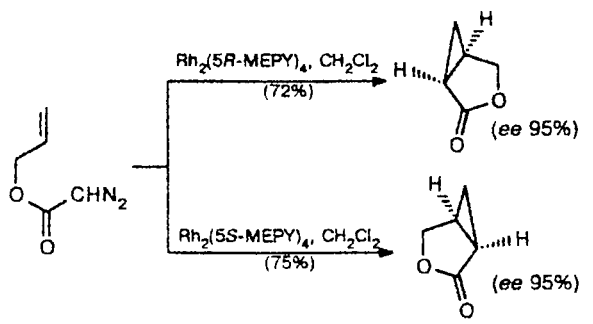
Diazo ketones with γ or δ double bonds undergo catalytic intramolecular cyclopropanation. These reactions occur with high enantiocontrol when catalyzed by copper semicorrins and bis-oxazolines, but low enantiocontrol characterizes reactions catalyzed by a broad selection of chiral dirhodium(II) carboxamidates. The reverse stereocontrol occurs for intramolecular cyclopropanation of allylic and homoallylic diazoacetates and diazoacetamides. This divergence is explained by conformational control of carbonyl alignment (*syn* or *anti* to the metal) of the metal carbene intermediate.

Key words: diazo ketones, enantioselective intramolecular cyclopropanation; chiral dirhodium(II) carboxamidates; chiral copper semicorrins; chiral copper bisoxazolines; metal carbenes.

The ability of chiral Rh^{II} carboxamidates to effectively catalyze intramolecular cyclopropanation of allylic diazoacetates[1–3] and diazoacetamides[4,5] with high enantiocontrol is well established.[6] In the simplest case, allyl diazoacetate, use of dirhodium(II) tetrakis[methyl 2-oxapyrrolidine-5*R*(or *S*)-carboxylate], Rh_2(5*R*-MEPY)$_4$ and Rh_2(5*S*-MEPY)$_4$, in catalytic amounts as low as 0.1 mol.% causes the formation of enantiomeric 3-oxabicyclo[3.1.0]hexan-2-ones (Scheme 1) with 95% enantiomeric excess (*ee*) in good yields following distillation.[2]

Scheme 1



* Dedicated to Academician of the RAS O. M. Nefedov (on his 65th birthday).

Consistently high levels of enantiocontrol (≥93% *ee*) are achieved with *cis*-disubstituted allylic diazoacetates and with trisubstituted systems, but with *trans*-disubstituted allylic diazoacetates use of the Rh_2(MEPY)$_4$ catalysts results in lower ee values. However, the steric bias provided by the class of *N*-acylimidazolidinone-ligated dirhodium(II) catalysts enhances enantiocontrol in these cases, so that with Rh_2(4*S*-MPPIM)$_4$ enantioselectivities are extended to ≥ 95%.[7] The same pattern of selectivity is achieved with the corresponding allylic diazoacetamides.

Three classes of dirhodium(II) carboxamidates have been prepared and characterized from chiral pyrrolidinone (**1**),[1,8] oxazolidinone (**2**)[9,10] and *N*-acylimidazolidinone (**3**) ligands,[11] four of which surround the dirhodium(II) core with *(cis*-2,2) geometry.

Attachments to the chiral center have been varied form carboxylate esters to alkyl and aryl groups, but only those with carboxylate ester attachments provide high enantiocontrol in intramolecular cyclopropanation reactions of diazoacetates and diazoacetamides.

With the exception of the recent report by Pfaltz and coworkers regarding applications of copper semicorrin complexes (**4**),[12] similar achievements of high enantiocontrol in intramolecular cyclopropanation reactions of diazo ketones have been generally absent. Early efforts with a chiral salicylaldimine-copper catalyst by Dauben[13] suggested that high enantiocontrol would be difficult to achieve, but only with **4** [12] (reaction (1)) and the corre-

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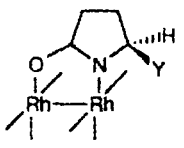
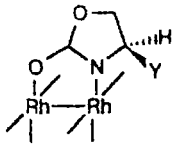


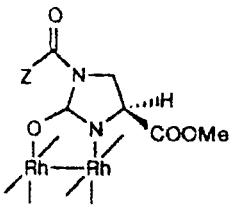
1

Y = COOMe: $Rh_2(5S\text{-MEPY})_4$
Y = $COOCH_2CMe_3$: $Rh_2(5S\text{-NEPY})_4$
Y = $CONMe_2$: $Rh_2(5S\text{-DMAP})_4$



2

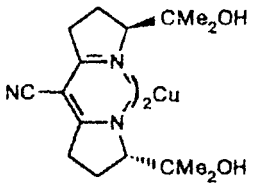
Y = CH_2Ph: $Rh_2(4R\text{-BNOX})_4$
Y = $CHMe_2$: $Rh_2(4R\text{-IPOX})_4$
Y = Ph: $Rh_2(4S\text{-PHOX})_4$
Y = COOMe: $Rh_2(4S\text{-MEOX})_4$



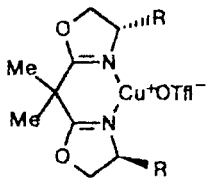
3

Z = Me: $Rh_2(4S\text{-MACIM})_4$
Z = Ph: $Rh_2(4S\text{-MBOIM})_4$
Z = CH_2CH_2Ph: $Rh_2(5S\text{-MPPIM})_4$

sponding bisoxazolines (**5**)[14] have high selectivities been realized, albeit in modest yields (*y*).

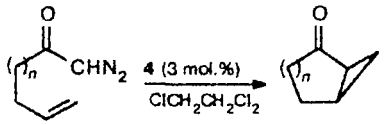


4



5a,b

R = Bu^t (**a**), $Me_2COSiMe_3$ (**b**)



(1)

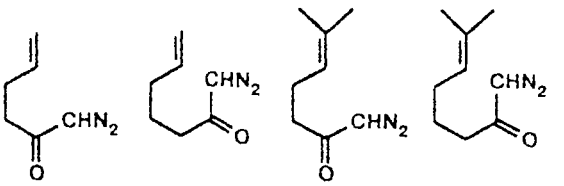
n	*y* (%)	*ee* (%)
1	50	75
2	55	94

We now report results from investigations of enantiocontrol in intramolecular cyclopropanation reactions of diazo ketones catalyzed by chiral dirhodium(II) carboxamidates. Comparison with results from diazoacetates demonstrates unique advantages for chiral copper catalysts in cyclizations of diazo ketones and advantages for chiral dirhodium(II) catalysts in cyclizations of diazoacetates and diazoacetamides that are interpreted as due to conformational control of metal carbene alignment.

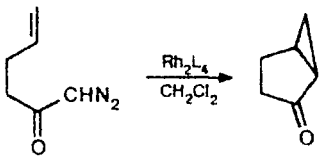
Results and Discussion

Diazo ketones **6**—**9** were prepared from the corresponding acid chlorides by reaction with excess diazomethane. Diazo decomposition of diazoketone **6** was investigated with a comprehensive series of chiral dirhodium carboxamidates (reaction (2)), and results from these reactions are reported in Table 1.

The yields of cyclopropane products are generally high, but enantioselectivity is low. The highest *ee* values



6 **7** **8** **9**



(2)

6 **10**

are obtained with the use of oxazolidinone-ligated dirhodium(II) catalysts whose chiral attachment is either benzyl, $Rh_2(BNOX)_4$, or isopropyl, $Rh_2(IPOX)_4$. In contrast, these same catalysts give relatively low levels of enantiocontrol in intramolecular cyclopropanation reactions of diazoacetates and diazoacetamides.[1] With diazoketone **7** even lower levels of enantioselectivity for intramolecular cyclopropanation were observed using $Rh_2(4S\text{-BNOX})_4$ (56% yield, 2% *ee*) or $Rh_2(5S\text{-MEPY})_4$ (58% yield, 6% *ee*). Using complex **4**, Pfaltz has shown

Table 1. Enantioselectivity in the catalytic decomposition of diazoketone **6**

Catalyst	Product **10**	
	Yield (%)	*ee* (%)
$Rh_2(5R\text{-MEPY})_4$	82	11
$Rh_2(5S\text{-NEPY})_4$	50	3
$Rh_2(5S\text{-DMAP})_4$	77	6
$Rh_2(4S\text{-BNOX})_4$	83	20
$Rh_2(4S\text{-IPOX})_4$	85	23
$Rh_2(4S\text{-PHOX})_4$	94	12
$Rh_2(4S\text{-MEOX})_4$	67	8
4	50	75[12]

Note. Reactions were performed at room temerature in CH_2Cl_2.

Table 2. Enantioselectivity in the catalytic decomposition of diazoketone **8**

Catalyst	Product **11**	
	Yield(%)	*ee* (%)
Rh_2(4*S*-MEPY)$_4$	84	4
Rh_2(4*S*-MEOX)$_4$	80	27
Rh_2(4*S*-MBOIM)$_4$	63	16
Rh_2(4*S*-MPPIM)$_4$	66	11
4	58	85[12]

Note. Reactions were performed in refluxing CH_2Cl_2.

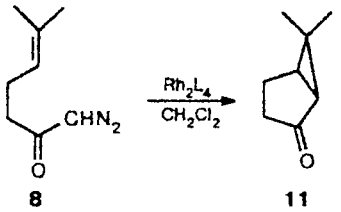
Table 3. Enantiocontrol in the catalytic intramolecular cyclopropanation of diazoacetate **14**

Catalyst	Product **15**, *ee* (%)	Catalyst	Product **5**, *ee* (%)
Rh_2(5*S*-MEPY)$_4$	98	Rh_2(4*S*-PHOX)$_4$	68
Rh_2(5*S*-DMAP)$_4$	44	Rh_2(4*S*-MEOX)$_4$	98
Rh_2(4*R*-BNOX)$_4$	56	Rh_2(4*S*-MACIM)$_4$	52
Rh_2(4*S*-IPOX)$_4$	43	**5a***	13

Note. Reactions were performed in CH_2Cl_2; yields ≥ 52%.
* $CuPF_6$/bisoxazoline.

that compound **10** could be formed with 75% *ee*, and the cyclopropane produced from **7** had 94% *ee*.[12]

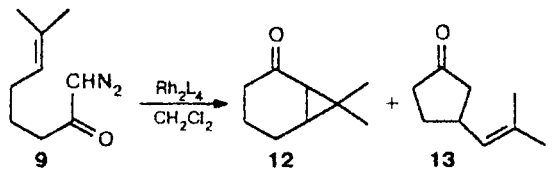
Intramolecular cyclopropanation of diazoketone **8** catalyzed by a similar series of chiral dirhodium(II) carboxamidates (reaction (3)) gave results that are reported in Table 2.



8 **11** (3)

In this series the Rh_2(4*S*-MEOX)$_4$ catalyst provided the highest level of enantiocontrol but, just as was found in reactions of diazoketone **6**, there is no apparent pattern that would suggest a unique catalyst design that could lead to enhanced enantiocontrol. Using complex **4** Pfaltz was able to achieve 85% *ee* with this system.[12]

With the higher homolog **9** intramolecular cyclopropanation occurred in competition with C—H insertion (reaction (4)), and this observation is consistent with the chemoselectivity of dirhodium(II) catalysts, which favors C—H insertion in reactions of diazo ketones.[15] However, similar C—H insertion is not observed for reactions of diazoketone **7**. Pfaltz reported that compound **12** was formed in 50% yield and 14% *ee* in reactions of diazoketone **9** catalyzed by complex **4**, but the production of compound **13** as a byproduct was not described.[12]

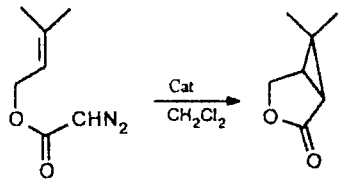


9 **12** **13** (4)

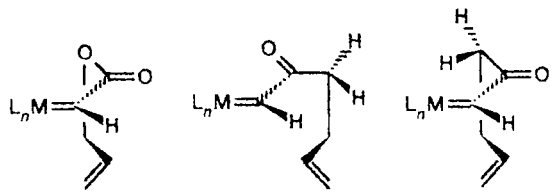
Cat	*y** (%)	[**12**] (*ee*) (%)	[**13**] (*ee*) (%)
Rh_2(5*S*-MEPY)$_4$	67	76 (17)	24 (1)
Rh_2(4*S*-MPPIM)$_4$	75	71 (8)	29 (8)

* Total yield

Although relatively ineffective for cyclizations of diazo ketones, chiral dirhodium(II) carboxamidates are the catalysts of choice for intramolecular cyclopropanation of allylic and homoallylic diazoacetates and diazoacetamides. Table 3 provides *ee* values from intramolecular cyclopropanation reactions of diazoketone **14** with a series of chiral catalysts (reaction (5)) for comparison with those reported in Tables 1 and 2. Formally, the only difference between diazoketones **14** and **8** is O *vs.* CH_2, yet the outcome from Cu^I and Rh^{II} catalysis is extreme. Whereas we have interpreted dirhodium(II)-catalyzed cyclization of allylic diazoacetates as occurring through metal carbene conformation **16**,[2] the corresponding diazo ketones may undergo intramolecular cyclopropanation through conformation **17** rather than **18**, the difference being whether the carbonyl group is *anti* or *syn* to the metal carbene M=C bond.



14 **15** (5)



16 **17** **18**

If **17** is the conformational alignment, cyclization occurs at a greater distance from the enantiocontrolling chiral ligands of the catalyst, and *ee* values are expected to be low as indeed they are with chiral dirhodium(II) carboxamidates. Thus conformational control of carbene alignment explains the extreme differences observed between chiral copper and rhodium catalysts and suggests design characteristics for catalysts that could enhance enantiocontrol.

Experimental

NMR spectra (in $CDCl_3$) were recorded on a Varian VXR 300 spectrometer, internal standard — $SiMe_4$. The other instrumentation used for analyses has been described.[16] The preparation and characterization of dirhodium(II) catalysts have been reported.[1,8–11] The preparation of diazo ketones **6—9** from the corresponding carboxylic acid chlorides and excess diazomethane followed standard procedures.[17] Anhydrous dichloromethane was distilled from CaH_2 prior to use.

Diazo decomposition (general procedure). A diazo ketone (1.00 mmol) in 5 mL of CH_2Cl_2 was added to solution of the dirhodium(II) catalyst (1.0 mol.%) in 15 mL of anhydrous CH_2Cl_2 at ~20 °C by controlled addition over an 8-h period. After addition was complete, the reaction mixture was filtered through a short plug of silica gel to remove the catalyst, and the plug was then washed with an additional 20 mL of CH_2Cl_2. The solvent was removed and the residue was analyzed directly by NMR and GC methods. Distillation provided a clear colorless oil, which was again subjected to chromatographic and spectral analyses. Enantiomer separations were performed by GC with baseline resolution on a 30-m Chiraldex G-TA column for analyses of products form **6—8** and on a 30-m Chiraldex A-DA column for analysis of products form **9**. The diazo compounds and their cyclopropanation products have been previously characterized.[4,12]

3-(2-Methyl-2-propen-1-yl)cyclopentanone (13). ^1H NMR (300 MHz, $CDCl_3$), δ: 5.06 (d hept, 1 H, J = 7.2, 1.4 Hz), 3.07—2.92 (m, 1 H); 2.40—2.24 (m, 2 H); 2.21—2.05 (m, 2 H); 1.92—1.81 (m, 1 H); 1.69 (s, 3 H); 1.64 (s, 3 H); 1.68—1.56 (m, 1 H).

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