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ENANTIOSELECTIVE CATALYTIC INTRAMOLECULAR CYCLOPROPANATION OF ALLYLIC α-DIAZOPROPIONATES OPTIMIZED WITH DIRHODIUM(II) TETRAKIS[METHYL 2-OXAZOLIDINONE-4(*S* OR *R*)-CARBOXYLATE]

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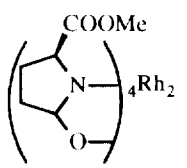
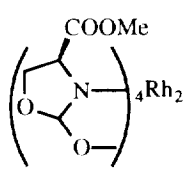
Summary: *High enantiocontrol, up to 85% ee, has been achieved in intramolecular cyclopropanation reactions of representative allylic α-diazopropionates with the catalytic uses of Rh_2(4S-MEOX)$_4$.*

Asymmetric catalytic cycloaddition of electrophilic metal carbenes to alkenes is a facile methodology for highly enantioselective cyclopropane syntheses.[1-3] Intramolecular reactions with allylic diazoacetates using catalytic amounts of dirhodium(II) tetrakis[methyl 2-oxapyrrolidine-5(*S* or *R*)-carboxylate], Rh_2(5*S*-MEPY)$_4$ or Rh_2(5*R*-MEPY)$_4$, produce the corresponding cyclopropane-fused bicyclic lactones in good yields and, generally, with exceptionally high levels of enantiocontrol (≥ 94% ee).[4] Analogous alkenyl diazomethyl ketones undergo intramolecular cyclopropanation catalyzed by chiral semicorrin-ligated copper in moderate yields and high enantioselectivities (up to 95% ee) in certain cases.[5] However, replacement of the hydrogen on the diazo carbon of a diazoacetate or a diazomethyl ketone by a larger substituent, typically COOMe, significantly decreases enantioselectivity so that the highest levels that have been achieved in cyclopropanation reactions are only 35-40% ee;[5-7] the implication is that there are severe constraints on enantioselectivity for formation of cyclopropane derivatives possessing a quaternary center alpha to the carbonyl group. α-Diazopropionates are more reactive than α-diazo-β-ketoesters towards diazo decomposition and, although the intermediate carbene can undergo facile 1,2-hydrogen migration,[8] intramolecular carbonyl ylide and C-H insertion reactions of α-diazoalkyl ketones catalyzed by rhodium(II) carboxylates have been reported to occur with negligible or only modest competition from hydrogen migration.[9,10] We are now able to report that allylic α-diazopropionates undergo intramolecular cyclopropanation catalyzed by dirhodium(II) tetrakis[methyl 2-oxazolidinone-4(*S* or *R*)-carboxylate], Rh_2(4*S*-MEOX)$_4$ or Rh_2(4*R*-MEOX)$_4$, in good yields and with enantioselectivities up to 85% ee.

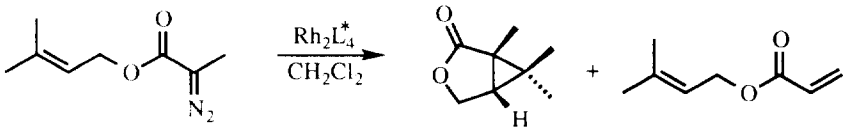


Rh_2(5*S*-MEPY)$_4$



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

Allylic α-diazopropinates were prepared in good yields by diazo transfer to allylic α-formylpropionates.[11] Diazo decomposition of the 3-methyl-2-buten-1-yl diazo ester (eq. 1) was evaluated for enantiocontrol in the formation of **2** with a selection of chiral dirhodium(II) catalysts that included carboxamidates and carboxylates (**4** and **5**), and the



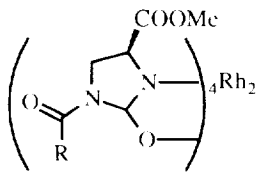
(1)

1 **2** **3**

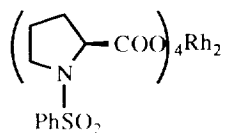
Table 1. Intramolecular cyclopropanation of **1**. Yield and % ee of **2** as a function of dirhodium(II) catalyst.[a]

catalyst	yield, %	% ee[b]	catalyst	yield, %	% ee[b]
Rh_2(5*S*-MEPY)$_4$	57	25	**4**	72	19
Rh_2(4*S*-MACIM)$_4$	71	52	**5**	83	6
Rh_2(4*S*-MPAIM)$_4$	63	63	Rh_2(4*S*-MEOX)$_4$	81	71
Rh_2(4*S*-MPPIM)$_4$	84	61[c]	Rh_2(4*R*-MEOX)$_4$	75	69[d]

[a]Reactions were performed in refluxing CH_2Cl_2 using 1.0 mol % of catalyst. With $Rh_2(OAc)_4$, 53% yield of **2**. [b]Baseline separation on a 30-m Chiraldex B-PH column operated at 100°C for 30 min, then programmed to 150°C at 0.2°/min: 43.5 min (minor isomer), 44.6 min (major isomer). [c]$[\alpha]_D^{23}$ = +47.9 (*c* 1.49, $CHCl_3$) for 61% ee. [d]Major isomer at 43.5 min on B-PH column.



R = Me, Rh_2(4*S*-MACIM)$_4$
R = CH_2Ph, Rh_2(4*S*-MPAIM)$_4$
R = CH_2CH_2Ph, Rh_2(4*S*-MPPIM)$_4$



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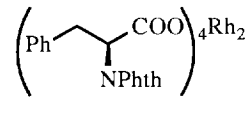
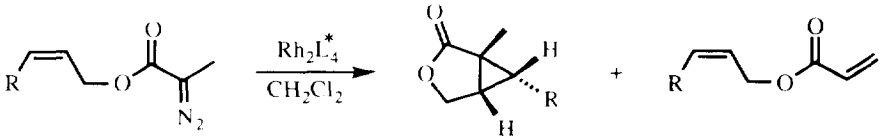


5

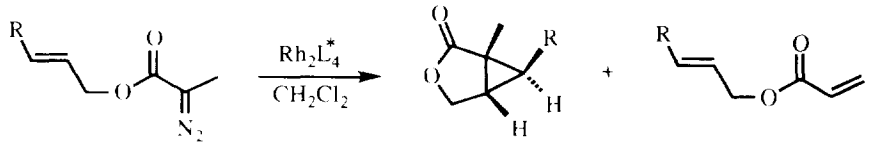
results are reported in Table 1. Neither the McKervey dirhodium(II) chiral prolinate **4**[12] nor the Ikegami chiral phthalimidate-phenyl alanate **5**[13] was as effective as any of the chiral dirhodium(II) carboxamidate catalysts, and, among the latter, Rh_2(4*S*-MEOX)$_4$ gave the highest level of enantiocontrol (71% ee).[14,15] 1,2-Hydrogen migration to form **3** was negligible or of minor importance (0-7%, except for Rh_2(4*S*-MPAIM)$_4$: 17%).

Extension of this methodology to *cis*-disubstituted allylic α-diazopropionates (**6a,b**) provided bicyclic lactones (eq. 2) with yields and enantiomeric excesses that are reported in Table 2. Like *cis*-disubstituted allylic diazoacetates, for which enantiomeric excesses of ≥ 94% ee were achieved with the use of Rh_2(MEPY)$_4$ catalysts,[4] diazo decomposition of **6a,b** also occurred with high enantiocontrol optimized with Rh_2(4*S*-MEOX)$_4$. With *trans*-disubstituted allylic α-diazopropionates (**6c,6d**), like *trans*-disubstituted allylic diazoacetates,[4] intramolecular cyclopropanation (eq. 3) occurred with lower enantiocontrol, even with Rh_2(4*S*-MEOX)$_4$. In these cases, but especially with **6c**, 1,2-hydrogen migration occurred in competition with intramolecular cyclopropanation.



6a, R = *n*-Pr
6b, R = Ph

7 **8** (2)



6c, R = *n*-Pr
6d, R = Ph

7 **8** (3)

Table 2. Intramolecular cyclopropanation of **6a-d**. Yield and % ee of **7a-d** as a function of dirhodium(II) catalyst.[a]

compound	R =	catalyst	yield **7** %	% ee **7**	yield **8**, %
a[b]	*n*-Pr	Rh_2(4*S*-MPAIM)$_4$	47	37[c]	18
	n-Pr	Rh_2(5*S*-MEPY)$_4$	87	59[c]	7
	n-Pr	Rh_2(4*S*-MEOX)$_4$	62	85[c,d]	20
b	Ph	Rh_2(4*S*-MPPIM)$_4$	57	36[e]	14
	Ph	Rh_2(5*S*-MEPY)$_4$	77	55[e]	5
	Ph	Rh_2(4*S*-MEOX)$_4$	65	78[e,f]	21
c	*n*-Pr	Rh_2(4*S*-MPAIM)$_4$	45	29[g]	18
	n-Pr	Rh_2(4*S*-MEOX)$_4$	46	52[g,h]	40
d	Ph	Rh_2(4*S*-MPAIM)$_4$	72	36[i]	9
	Ph	Rh_2(4*S*-MEOX)$_4$	70	43[i,j]	12

[a]Reactions were performed in refluxing CH_2Cl_2 using 1.0 mol % of catalyst. [b]Dirhodium(II) carboxylates produced **7a** in 91% yield (7% ee) with **4** and 90% yield (0% ee) with **5**. [c]Baseline separation on a 30-m Chiraldex G-TA column operated at 100°C for 60 min then programmed to 150° at 0.3°/min: 102.8 min (minor isomer), 104.6 min (major isomer). [d]$[\alpha]_D^{23}$ = +42.5 (*c* 0.40, $CHCl_3$) for 85% ee. [e]Baseline separation on a 30-m Chiraldex G-TA column operated at 150°C: 45.1 min (major isomer), 49.0 min (minor isomer). [f]$[\alpha]_D^{23}$ = -89.2 (*c* 1.11, $CHCl_3$) for 78% ee. [g]Baseline separation on a 30-m Chiraldex G-TA column operated at 100°C for 20 min then programmed to 150°C at 1°/min: 59.7 min (major isomer), 69.2 min (minor isomer) [h]$[\alpha]_D^{23}$ = +37.0 (*c* 1.0, $CHCl_3$) for 52% ee. [i]Baseline separation on a 30-m Chiraldex G-TA column operated at 150°C: 63.0 min (major isomer), 81.2 min (minor isomer). [j]$[\alpha]_D^{23}$ = +26.4 (*c* 0.55, $CHCl_3$) for 43% ee

Enantiocontrol from intramolecular cyclopropanation of allylic α-diazopropionates parallels that from reactions of allylic diazoacetates.[4] The relative effectiveness of Rh_2(4*S*-MEOX)$_4$ is due, at least in part, to the openness of the volume segment of the catalyst that can accommodate the methyl substituent of the carbene. This openness, which follows the order Rh_2(4*S*-MEOX)$_4$ > Rh_2(5*S*-MEPY)$_4$ > Rh_2(4*S*-MACIM)$_4$ and other imidazolidinone-ligated catalysts, is suggested by the X-ray crystal structures for the nitrile complexes of these chiral dirhodium(II) carboxamidates[14,17] and is reflected in the % ee values obtained from their use. Increasing the size of the carbene substituent

from Me (in **1** and **6**) to Ph was expected to significantly diminish enantiocontrol, and this has been realized in intramolecular cyclopropanation of phenyldiazoacetate analogs of **6c,d** (8-26% ee when R = *n*-Pr, < 3% ee and incomplete reaction when R = Ph).

The extent of 1,2-hydrogen migration is highest with $Rh_2(4S\text{-MEOX})_4$ and lowest for $Rh_2(5S\text{-MEPY})_4$. In addition, the yield of **8** is higher with 3-alkyl substituents on the allylic double bond than with phenyl. Dirhodium(II) carboxylates reduce the importance of **8** further. The competition between **7** and **8** appears to be due to both electronic and steric factors, and continuing efforts are being directed to improving enantioselection while reducing the importance of 1,2-hydrogen migration.

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