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Optimization of enantiocontrol in *cis*-selective cyclopropanation reactions catalyzed by dirhodium(II) tetrakis[alkyl 2-oxaazetidine-4(*S*)-carboxylates]

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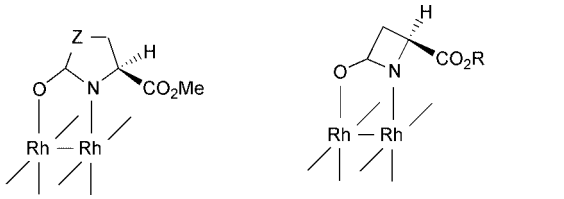
Both intermolecular and macrocyclic intramolecular cyclopropanation reactions occur with greater selectivity for the *cis*-(*Z*)-diastereoisomer than for the *trans*-(*E*)-diastereomer in reactions catalyzed by chiral dirhodium(II) azetidinonecarboxylates; the influence of the catalyst's ester alkyl group on enantiocontrol is substantial but appears to be delicately balanced by steric factors.

Chiral dirhodium(II) carboxamidate catalysts having the general structural framework of **1** have been widely employed to achieve high diastereoselectivity and enantiocontrol in a wide variety of catalytic metal carbene transformations.[1–3] The

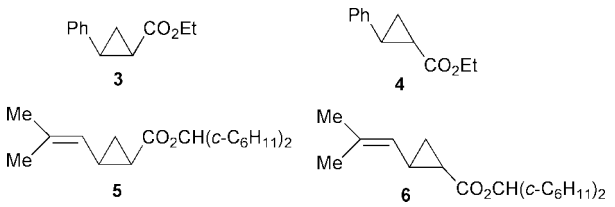


1a Z = CH_2: Rh_2(5*S*-MEPY)$_4$
1b Z = O: Rh_2(4*S*-MEOX)$_4$
1c Z = $NCOCH_2CH_2Ph$: Rh_2(5*S*-MPPIM)$_4$

2a R = Bu^i: Rh_2(4*S*-IBAZ)$_4$
2b R = Bn: Rh_2(4*S*-BNAZ)$_4$
2c R = Me: Rh_2(4*S*-MEAZ)$_4$
2d R = CH_2CMe_3: Rh_2(4*S*-NEPAZ)$_4$
2e R = *c*-C_6H_{11}: Rh_2(4*S*-CHAZ)$_4$

methyl ester has been commonly employed because early investigations showed no significant difference in enantiocontrol with ester variation from methyl to octadecyl and from isopropyl to neopentyl.[4–6] However, we recently reported the preparation of two chiral azetidinone-4-carboxylate-ligated dirhodium(II) catalysts, Rh_2(4*S*-IBAZ)$_4$ **2a** and Rh_2(4*S*-BNAZ)$_4$ **2b**, whose ester alkyl group seemed to have a significant influence on enantiocontrol in cyclopropanation[7] and insertion[8] transformations. We now report, from results obtained with a broad selection of these catalysts, that the size of the ester alkyl group has a modest influence on diastereoselectivity but has a substantial, but irregular, effect on enantiocontrol in addition reactions.

The catalytic reaction of ethyl diazoacetate (EDA) with styrene is the classic transformation with which stereoselectivity for cyclopropanation is measured and catalyst effectiveness is determined.[1,9] Products are *cis*- and *trans*-2-phenylcyclopropanecarboxylate esters **3** and **4**.



3 **4** **5** **6**

Chiral copper, ruthenium and cobalt catalysts show a marked preference for the *trans* isomer **4**, and this is also true for application of the dirhodium carboxamidate catalyst **1a**.[1,9] An exception is the Ru–salen catalyst recently reported by Katsuki and co-workers.[10] However, the use of chiral azetidinone catalysts **2** provides a distinct preference for the thermodynamically less stable **3** (Table 1), and enantiocontrol for the favored isomer is quite respectable. With 4-methylpenta-l,3-diene and dicyclohexylmethyl diazoacetate (DCDA)[11] these same catalysts show exclusive regioselection for addition to the less-substituted double bond (**5** + **6**), comparable diastereocontrol to that obtained with styrene/EDA, and exceptional enantiocontrol in the formation of **5**. The absolute configuration for the major isomer of **3** (and **5**) is (1*S*, 2*R*); that for **4** (and **6**) is (1*S*, 2*S*).

Table 1 Stereocontrol in intermolecular asymmetric cyclopropanation reactions catalyzed by **2**[a]

Catalyst	Isolated yield (%)[b]	**3**:**5**(**5**:**6**)	Ee(%) **3**(**5**)	Ee(%) **4**(**6**)
$PhCH{=}CH_2$ + EDA:[c]				
Rh_2(4*S*-IBAZ)$_4$ **2a**	62	69:31	76	52
Rh_2(4*S*-BNAZ)$_4$ **2b**	74	58:42	60	32
Rh_2(4*S*-MEAZ)$_4$ **2c**	65	55:45	58	32
Rh_2(4*S*-NEPAZ)$_4$ **2d**	69	66:34	67	34
Rh_2(4*S*-CHAZ)$_4$ **2e**	68	64:36	70	50
$Me_2C{=}CHCH{=}CH_2$ + DCDA:[d]				
Rh_2(4*S*-IBAZ)$_4$ **2a**[e]	81	54:46	>98	66
Rh_2(4*S*-BNAZ)$_4$ **2b**	89	42:58	>98	70
Rh_2(4*S*-MEAZ)$_4$ **2c**	86	43:57	91	63
Rh_2(4*S*-NEPAZ)$_4$ **2d**	91	49:51	>98	70
Rh_2(4*S*-CHAZ)$_4$ **2e**	80	53:47	83	60

[a] Reactions were performed in refluxing CH_2Cl_2 using 1.0 mol% catalyst. [b] Yield of **3** + **4** (or **5** + **6**) after chromatography. [c] [Styrene]/[EDA] = 10; % ee values obtained by GC on a 30 m Chiraldex B-DM column with *cis*-isomers eluting before *trans*-isomers. [d] [Diene]/[DCDA] = 4; % ee values obtained from the methyl esters following saponification and resterification with analysis on a 30 m Chiraldex G-TA column. [e] Data from ref. 7.

As can be seen from the data in Table 1, diastereoselectivity and enantioselectivity are responsive to the ester alkyl group of the catalyst ligand. Larger alkyl groups favor the *cis*-cyclopropanecarboxylate isomer more than do the smaller ones (**2b** and **2c**). In addition to suggesting the potential of **2** for predominant formation of highly enantioenriched *cis*-substituted cyclopropanecarboxylates, however, the data in Table 1 also allow us to correct data previously reported for Rh_2(4*S*-BNAZ)$_4$[7] which showed considerably lower enantioselectivities from those reported in Table 1.

Catalysts **1** have been shown to be particularly suitable for high enantiocontrol in intramolecular cyclopropanation reactions of allylic diazoacetates, providing the cyclized products in high yields and with ee values >94%.[1,3,12] With allyl diazoacetate **7**, for example, use of Rh_2(5*S*-MEPY)$_4$ **1a** gives the corresponding bicyclic lactone **8** in good yield and with 95% ee. In contrast, chiral azetidinones **2** do not have such high enantiocontrol in reactions with **7** (Table 2), but they do show a remarkable variation in % ee as a function of the ester alkyl group on the catalyst.

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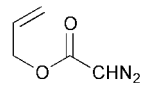

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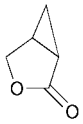

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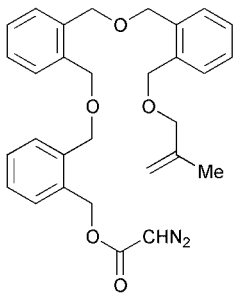
Table 2 Enantiocontrol in intramolecular asymmetric cyclopropanation reaction of allyl diazoacetate by **2**[a]

Catalyst	Isolated yield of **8** (%)[b]	Ee (%) of **8**[c]
Rh_2(4S-IBAZ)$_4$ **2a**	74	80
Rh_2(4S-BNAZ)$_4$ **2b**	70	56
Rh_2(4S-MEAZ)$_4$ **2c**	77	76
Rh_2(4S-NEPAZ)$_4$ **2d**	63	58
Rh_2(4S-CHAZ)$_4$ **2e**	90	68

[a] Reactions were performed in refluxing CH_2Cl_2 using 1.0 mol% catalyst. [b] Yield of **8** after chromatography. [c] Determined by GC on a 30 m Chiraldex G-PN column at 100 °C; the major isomer elutes first.

Macrocyclization in cyclopropanation reactions has recently been demonstrated to be a general transformation,[13] although less suitable for enantiocontrolled syntheses with catalysts **1** than with chiral copper(I) bis-oxazoline complexes.[14] In the limit, as the attachment of the carbon–carbon double bond to the diazoacetate becomes increasingly longer, enantioselectivity is expected to approach that obtained in the intermolecular transformation. To further evaluate the macrocyclization process, methallyl diazoacetate **9** was treated with each catalyst in the series of chiral dirhodium(II) azetidinones **2**. The (*Z*)- and (*E*)-cyclopropane products **10** were formed in high yield, and



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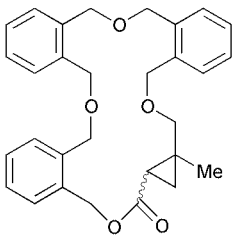

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% ee values for (*Z*)-**10** reached moderately high levels (Table 3). For comparison, intramolecular cyclopropanation of methallyl diazoacetate using Rh_2(4S-IBAZ)$_4$ formed the corresponding bicyclo[3.1.0]-derivative in 28% ee, which is consistent with our original hypothesis regarding enantiocontrol in macrocyclic cyclopropanation reactions.

Table 3 Stereocontrol in intramolecular asymmetric cyclopropanation reactions of **9** catalyzed by **2**[a]

Catalyst	Isolated yield of **10** (%)[b]	(*Z*)-**10**:(*E*)-**10**	Ee (%) of (*Z*)-**10**[c]
Rh_2(4S-IBAZ)$_4$ **2a**	64	78:22	69
Rh_2(4S-BNAZ)$_4$ **2b**	74	82:18	53
Rh_2(4S-MEAZ)$_4$ **2c**	78	78:22	56
Rh_2(4S-NEPAZ)$_4$ **2d**	64	82:18	62
Rh_2(4S-CHAZ)$_4$ **2e**	67	83:17	63

[a] Reactions were performed in refluxing CH_2Cl_2 using 1.0 mol% catalyst. [b] Yield of **10** following chromatography. [c] Determined following hydrogenolysis of **10** that converted (*Z*)-**10** to its bicyclo[3.1.0]-derivative with analysis performed by GC on a Chiraldex G-TA column.

The overall effectiveness of Rh_2(4S-IBAZ)$_4$ for the catalytic asymmetric cyclopropanation reactions reported here does not follow size considerations of the ligand's ester alkyl group. The isobutyl group is neither the largest nor the smallest alkyl group in the series. Yet in spite of differences exceeding 20% in enantiomeric excess, this catalyst consistently gives the highest level of enantiocontrol.

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