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# Dirhodium(II) Tetrakis[methyl 2-oxaazetidine-4-carboxylate]: A Chiral Dirhodium(II) Carboxamidate of Exceptional Reactivity and Selectivity

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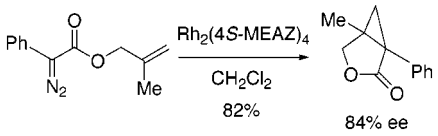
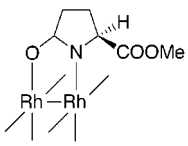
## ABSTRACT




**A new chiral azetidinone−carboxylate ligand for dirhodium(II) catalysts enhances reactivity toward diazo decomposition and selectivity toward cyclopropanation enabling diazomalonates, vinyldiazoacetates, and aryldiazoacetates to be effectively used with a dirhodium(II) carboxamidate catalyst.**

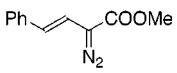
Dirhodium(II)[1,2] carboxamidates are notoriously unreactive toward diazo decomposition of substituted diazoacetates, especially $\beta$-carbonyl derivatives such as diazomalonate. With $Rh_2$(5*S*-MEPY)$_4$ (**1**), for example, diazo decomposition does not occur over extended periods with dimethyl diazomalonate even in refluxing 1,2-dichloroethane (bp 83 °C). Furthermore, Davies has reported that **1** failed to cause diazo decomposition of vinyldiazoacetate **2** (Scheme 1), but

**Scheme 1**




**1**

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




**2**

allowed instead intramolecular rearrangement to a pyrazole.[3] In contrast, the generally more reactive dirhodium(II) carboxylates and some copper(I) catalysts are amenable to reactions with these diazo compounds.[4−6] We now wish to report a new chiral catalyst whose reactivity toward diazo decomposition allows access to previously unreactive diazocarbonyl compounds and whose enantioselectivity in cyclopropanation suggests expanded uses for chiral dirhodium(II) carboxamidates in catalytic metal carbene transformations.

Catalytic diazo decomposition of dimethyl diazomalonate is not only a relatively difficult objective, often requiring temperatures in excess of 80 °C, but reactions with alkenes generally produce cyclopropane derivatives with low enantioselectivities. Davies reported 7% ee for the product from intermolecular cyclopropanation of styrene using dirhodium-

(1) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley: New York, 1998; Chapter 2.

(2) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911.

(3) Davies, H. M. L.; Huby, N. J. S.; Cantrell, W. R., Jr.; Olive, J. L. *Org. Chem.* **1993**, *58*, 9468.

(4) Davies, H. M. L.; Doan, B. D. *J. Org. Chem.* **1999**, *64*, 8501. For reviews of the effectiveness of chiral dirhodium(II) carboxylates with styryldiazoacetates in cyclopropanation reactions see: (a) Davies, H. M. L. *Aldrichim. Acta* **1997**, 107. (b) Davies, H. M. L. *Eur. J. Org. Chem.* **1999**, 2459.

(5) With chiral semicorrin−copper catalyst: Pique, C.; Fahndrich, B.; Pfaltz, A. *Synlett.* **1995**, 491.

(6) With a chiral bisoxazoline−copper catalyst: Koskinen, A. M. P.; Hassila, H. *J. Org. Chem.* **1993**, *58*, 4479.

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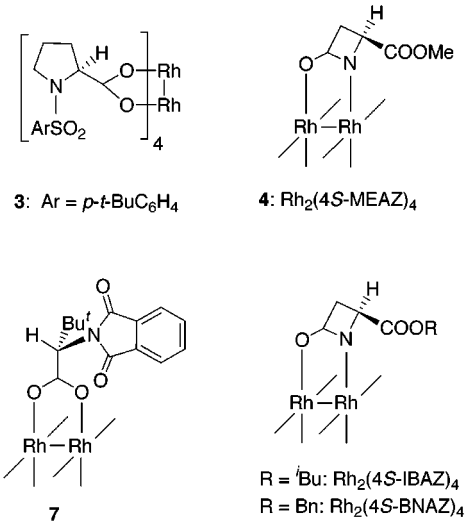
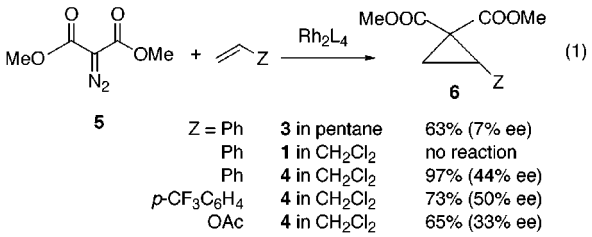
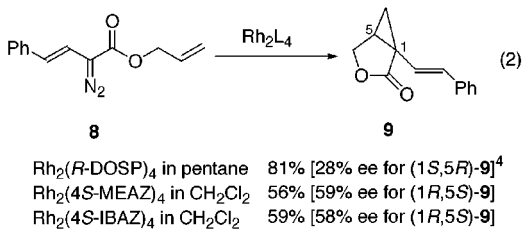
(II) (*S*)-*N*-(arylsulfonyl)prolinate **3**,[7] and for intramolecular cyclopropanation of allyl $\beta$-ketoesters the highest enantiomeric excesses yet reported were 35-40%.[5,6] Thus, we were surprised to discover that dirhodium(II) tetrakis[methyl 2-oxaazetidine-4(*S*)-carboxylate], $Rh_2$(4*S*-MEAZ)$_4$ (**4**, Scheme 2), was an effective catalyst for cyclopropanation reactions

**Scheme 2**




with dimethyl diazomalonate. Reactions occurred cleanly and in high yield in refluxing dichloromethane. Enantiocontrol (up to 50% ee) was the highest yet reported (eq 1), and even for cyclopropanation of the highly reactive and normally unselective vinyl acetate the enantiometric excess of the cyclopropanation product was 33%. Hashimoto's dirhodium *tert*-leucinate catalyst (**7**)[8] applied to eq 1 resulted in the formation of **6** in 88% yield, but with only 23% ee (Z = Ph).

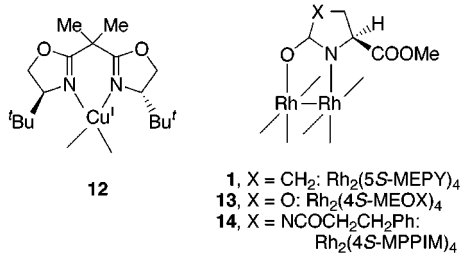



The dirhodium(II) carboxamidate $Rh_2$(4*S*-MEAZ)$_4$ belongs to the family of chiral azetidinone-ligated catalysts first reported in 1996 bearing the isobutyl and benzyl esters, $Rh_2$(4*S*-IBAZ)$_4$ and $Rh_2$(4*S*-BNAZ)$_4$.[9] The X-ray structure of $Rh_2$(4*S*-BNAZ)$_4$ describes an unusually long Rh−Rh bond that, we suggest, is a consequence of ligand strain on the dirhodium(II) framework that results in higher reactivity toward diazo decomposition relative to **1**. The influence of the ligand ester on % ee is measurable, and $Rh_2$(4*S*-MEAZ)$_4$ is generally more selective than either $Rh_2$(4*S*-IBAZ)$_4$ or $Rh_2$(4*S*-BNAZ)$_4$ (38% ee and 25% ee, respectively, in eq 1 with styrene). The azetidinone ligand of **4** was prepared in 93% yield by esterification of 2-oxaazetidine-4(*S*)-carboxylic acid with diazomethane,[10] and $Rh_2$(4*S*-MEAZ)$_4$ was synthesized in 53% yield (after purification) from $Rh_2(OAc)_4$ and an 8-fold molar excess of ligand in refluxing (5 h) chlorobenzene.[11]

Extended applications of the azetidinone-ligated dirhodium(II) catalysts have shown that they are also amenable to diazo decomposition of vinyldiazoesters. Treatment of **8** with $Rh_2$((*R*)-DOSP)$_4$ (**3**, Ar = *p*-$CH_3(CH_2)_{11}C_6H_4$) has recently been shown to effect intramolecular cyclopropanation in good yield but with low enantioselectivity (eq 2).[4] In contrast, the chiral azetidinone-ligated catalysts $Rh_2$(4*S*-MEAZ)$_4$ and $Rh_2$(4*S*-IBAZ)$_4$ both effected significantly higher enantio-control. Comparable studies with the corresponding phenyldiazoacetate (eq 3) demonstrated an even higher level of enantiocontrol. In all of these studies, % ee values were determined by gas chromatography with baseline resolution on Chiraldex columns. Yields were determined by weight after chromatography. It is notable that use of chiral copper(I) bisoxazoline catalyst **12**[12] with **10** gave a low yield of the intramolecular cyclopropanation product (36%), with dimer formation being a major competing process (40% yield), and the enantiomeric excess of the cyclopropane compound was expectedly low.[13] Of the alternative chiral dirhodium(II) carboxamidates (Scheme 3), only $Rh_2$(5*S*-MEPY)$_4$ gave a

**Scheme 3**




reasonable yield of product from reaction with **10** (46%), the product yields from use of $Rh_2$(4*S*-MEOX)$_4$ (**13**) or $Rh_2$-

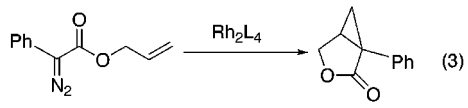
(7) Davies, H. M. L.; Bruzinski, P.; Fall, M. J. *Tetrahedron Lett*. **1996**, *37*, 4133.

(8) Watanabe, N.; Ogawa, T.; Ohtake, Y.; Ikegami, S.; Hashimoto, S. *Synlett* **1996**, 85.

(9) Doyle, M. P.; Zhou, Q.-L.; Simonsen, S. H.; Lynch, V. *Synlett* **1996**, 697.

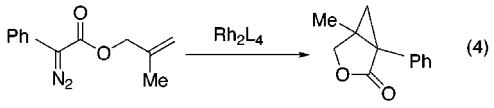
(10) $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.67 (brs, 1H), 4.20 (dd, $J$ = 6.0, 2.4 Hz, 1H), 3.79 (s, 3H), 3.33 (ddd, $J$ = 15.0, 6.0, 1.5 Hz, 1H), 3.07 (ddd, $J$ = 15.0, 2.4, 1.5 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 171.5, 166.6, 52.5, 47.1, 43.4; $[\alpha]^{23}_D$ = −51.9 (*c* 0.7, $CH_2Cl_2$).

(4*S*-MPPIM)$_4$ (**14**) being less than 20%, but with each of these catalysts enantiomeric excesses for the cyclopropane product were less than 5%.



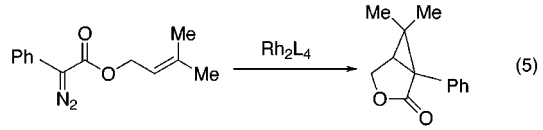

**10** **11**

| | |
|---|---|
| **3** in $CH_2Cl_2$ | 92% (28% ee) |
| **3** in pentane | 93% (36% ee) |
| $Rh_2$(4*S*-MEAZ)$_4$ in $CH_2Cl_2$ | 80% (68% ee) |
| $Rh_2$(4*S*-IBAZ)$_4$ in $CH_2Cl_2$ | 83% (64% ee) |




**15** **16**

| | |
|---|---|
| **3** in $CH_2Cl_2$ | 90% (29% ee) |
| **3** in hexane | 77% (51% ee) |
| $Rh_2$(4*S*-MEAZ)$_4$ in $CH_2Cl_2$ | 82% (84% ee) |
| $Rh_2$(4*S*-IBAZ)$_4$ in $CH_2Cl_2$ | 80% (68% ee) |




**17** **18**

| | |
|---|---|
| **3** in $CH_2Cl_2$ | 76% (29% ee) |
| **3** in pentane | 85% (44% ee) |
| $Rh_2$(4*S*-MEAZ)$_4$ in $CH_2Cl_2$ | 93% (45% ee) |
| $Rh_2$(4*S*-IBAZ)$_4$ in $CH_2Cl_2$ | 92% (19% ee) |

By analogy with results obtained by Davies,[4] the absolute configuration of **9** formed through catalysis by $Rh_2$(4*S*-MEAZ)$_4$ or $Rh_2$(4*S*-IBAZ)$_4$ was opposite to that obtained with $Rh_2$(*R*-DOSP)$_4$. In other words, the principal enantiomer formed with dirhodium(II) carboxamidate catalysts having the oxaazetidine-4(*S*)-carboxylate ligands had the (1*R*,5*S*)-absolute configuration that is depicted in eq 2. Chromatographic analyses on chiral GC columns show that **3** provides products **9**, **11**, **16**, and **18** with the same absolute configurations as does **4**.

Two additional cyclopropanation reactions exemplify the relative advantages of the uses of these catalysts. A striking comparison is seen in the results from diazo decomposition of phenyldiazoacetate **15**, which results in the formation of a cyclopropane product having two adjacent quaternary centers (eq 4). Here, carboxamidate $Rh_2$(4*S*-MEAZ)$_4$ (**4**) is superior to carboxylate **3** by a wide margin, and the product formed using this azetidinone catalyst was, after one recrystallization, enantiomerically pure (>99.9% ee). A second example is diazo decomposition of **17** (eq 5) in which enantiocontrol from **3** is the same as that from $Rh_2$(4*S*-MEAZ)$_4$. Here the overall low % ee values may reflect steric influences from the terminal dimethyl and phenyl substituents since with the styryldiazoacetate analogues corresponding to **8**, much higher % ee values for **3** were realized.[4]

Note that, as Davies originally observed,[14] enantioselectivities from the use of **3** in pentane are higher than those for reactions performed in dichloromethane. However, as seen from the data for eqs 3−5, the differences are highly variable. In contrast, and reflecting the rigidity of their structures,[1] the chiral dirhodium(II) carboxamidates show no variability in % ee values as a function of solvent.[15]

With regard to catalyst reactivity toward diazo decomposition, $Rh_2$(4*S*-MEAZ)$_4$ does not react with diazo esters at −78 °C. Those dirhodium(II) carboxylate catalysts employed by Davies are active at these low temperatures.[4]

In summary, the chiral 2-oxaazetidine-4-carboxylate-ligated dirhodium(II) catalysts, but especially $Rh_2$(4*S*-MEAZ)$_4$, offers high potential to significantly broaden the applicability of diazocarbonyl compounds for asymmetric synthesis.

**Acknowledgment.** We are grateful to the National Science Foundation and to the National Institutes of Health (GM 46503) for their support of this research.

**Supporting Information Available:** Experimental and spectral data that include the synthesis of $Rh_2$(4*S*-MEAZ)$_4$ and diazo compounds, their characterization, and those of the reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) $^{13}$C NMR of bis-acetonitrile complex (125 MHz, $CDCl_3$) $\delta$ 188.8, 188.2, 173.4, 173.3, 115.3, 52.9, 52.1, 51.9, 43.5, 42.6, 2.4; $[\alpha]^{24}_D = -214$ (*c* 0.7, $CH_3CN$).

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

(13) Doyle, M. P.; Peterson, C. S.; Zhou, Q.-L.; Nishiyama, H. *J. Chem. Soc., Chem. Commun*. **1997**, 211.

(14) Davies, H. M. L.; Hutcheson, D. K. *Tetrahedron Lett*. **1993**, *34*, 7243.

(15) Doyle, M. P.; Zhou, Q.-L.; Charnsangavej, C.; Longoxsria, M. A.; McKervey, M. A.; Garcia, C. F. *Tetrahedron Lett*. **1996**, *37*, 4129.